

Title of the Invention

AZA-BRIDGED-BICYCLIC AMINO ACID DERIVATIVES AS α_4 INTEGRIN ANTAGONISTS

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Field of the Invention

This patent application claims benefit of US Patent Application Serial Number 60/215,695 filed on June 30, 2000 entitled "AZA-BICYCLIC AMINO ACID DERIVATIVES AS α_4 INTEGRIN ANTAGONISTS", which is hereby incorporated by reference. This invention relates to novel compounds and methods for use in treating integrin mediated disorders. More particularly, this invention relates to novel derivatives of aza-bridged-bicyclic amino acid compounds useful as α_4 integrin receptor antagonists, methods for treating integrin mediated disorders including, but not limited to, inflammatory, autoimmune and cell-proliferative disorders, methods for preparing the compounds and methods for preparing the intermediates, derivatives and pharmaceutical compositions thereof.

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Background of the Invention

Integrin receptors are transmembrane, non-covalently linked heterodimers consisting of one α -chain and one β -chain. In addition to performing a structural adhesive function, integrin receptors transmit extracellular signals across the plasma membrane. The integrin receptor $\alpha_4\beta_1$ (also referred to as VLA-4) mediates cell adhesion by binding with either of two protein ligands: vascular cell adhesion molecule-1 (VCAM-1) (Osborn, L.; et al., *Cell*, **1989**, 59, 1203), or the alternatively-spliced fibronectin variant containing the type III connecting segment (CS-1) (Wayner, E. A.; et al., *Cell Biol.*, **1989**, 109, 1321). In contrast to the prototypical integrin receptors $\alpha_5\beta_1$, GPIIb/IIIa and $\alpha_v\beta_3$ that recognize the Arg-Gly-Asp (RGD) tripeptide sequence in their respective ligands, $\alpha_4\beta_1$ binds to other primary protein sequences. The $\alpha_4\beta_1$

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integrin receptor recognizes Gln-Ile-Asp-Ser (QIDS) in VCAM-1 and Ile-Leu-Asp-Val (ILDV) in fibronectin. Although these sequences share a conserved Asp residue with RGD, they are otherwise unrelated. Additionally, recent studies have found that $\alpha_4\beta_1$ binds the matrix ligand osteopontin (Bayless, K. J.; et al., *J. Cell Sci.*, **1998**, *111*, 1165). The osteopontin ligand interaction with the $\alpha_4\beta_1$ receptor may be very important as osteopontin is strongly up-regulated in inflammatory settings, including the inflamed lung.

The $\alpha_4\beta_1$ integrin receptor is expressed at high levels on mast cells, mononuclear leukocytes, eosinophils, macrophages, and basophils (Adams, S. P.; et al., *Ann. Rep. Med. Chem.*, **1999**, *34*, 179). The binding of $\alpha_4\beta_1$ to cytokine-induced VCAM-1 on high-endothelial venules at sites of inflammation results in leukocyte/endothelium adhesion followed by extravasation into the inflamed tissue (Chuluyan, H. E.; et al., *Springer Semin. Immunopathol.*, **1995**, *16*, 391). The role of mast cells and eosinophils in lung inflammation is well-established. Induction of VCAM-1 expression on airway endothelial cells seems to play a central role in lung inflammation. The $\alpha_4\beta_1$ receptor interaction with VCAM-1 also exerts an important effect in stem cell adhesion to bone marrow stromal cells (Simmons, P. J.; et al., *Blood*, **1992**, *80*, 388).

The $\alpha_4\beta_7$ integrin is expressed at high levels on lymphocytes and T cells. The trafficking of lymphocytes from the vasculature to normal mucosa and lymphoid tissues is mediated by adhesion of mucosal addressing cell adhesion molecule-1 (MAdCAM-1) with the integrin receptor $\alpha_4\beta_7$. In an inflammatory setting, MAdCAM-1, an immunoglobulin superfamily adhesion molecule, specifically binds $\alpha_4\beta_7$ -expressing lymphocytes and participates in the homing of these cells to the mucosal endothelium. Cloning studies of human MAdCAM-1 have shown that the Leu-Asp-Thr-Ser-Leu (LDTSL) sequence of the CD loop is conserved. In fact, LDT-based peptides bind to $\alpha_4\beta_7$ in a MAdCAM-1/RPMI-8866 cell adhesion assay with IC_{50} values in the 1-10 μ M range (Shroff, H. N.; et al., *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 1601).

The extensive biology mediated by integrins in general and compelling data for the pathophysiological role of the leukocyte cell adhesion receptor $\alpha 4 \beta 1$ have spurred interest in the study of $\alpha 4 \beta 1$ antagonists in vivo. Cellular adhesion and migration mediated through the $\beta 1$ integrins are critical components of cellular recruitment processes. The integrin $\alpha 4 \beta 1$ provides a key co-stimulatory signal supporting cell activation leading to growth factor and cytokine production and mediator release. Through recognition of the extracellular matrix, $\alpha 4 \beta 1$ increases the survival of activated cells by inhibiting apoptosis (Yoshikawa, H.; et al., *J. Immunol.*, **1996**, 156, 1832).

Monoclonal antibodies directed against $\alpha 4 \beta 1$ or VCAM-1 have been shown to be effective modulators in animal models of chronic inflammatory diseases such as asthma (Laberge, S.; et al., *Am. J. Respir. Crit. Care Med.*, **1995**, 151, 822), rheumatoid arthritis (Barbadillo, C.; et al., *Springer Semin. Immunopathol.*, **1995**, 16, 375) and inflammatory bowel disease (Powrie, F.; et al., *Ther. Immunol.*, **1995**, 2, 115). The initial research in the low molecular weight $\alpha 4 \beta 1$ antagonist arena has focused on simple linear analogues of the prototype Leu-Asp-Val sequence. Phenylacetyl-Leu-Asp-Phe-D-Pro-NH₂ (having an $\alpha 4 \beta 1$ IC₅₀ value of 2 uM) exhibited efficacy similar to the $\alpha 4$ antibody PS/2 in a mouse model of oxazolone-induced contact hypersensitivity when administered at 6 mg/kg, sc (Tamraz, S.; et al., *Springer Semin. Immunopathol.* **1995**, 16, 437). This tetrapeptide was also effective in a hyperlipidemic rabbit heterotopic heart allograft model (Molossi, S.; et al., *J. Clin. Invest.* **1995**, 95, 2601).

Animal models of asthma have shown that the peptide antagonist BIO-1211 inhibits eosinophilia and airway hyperresponsiveness (Lin, K-C.; et al., *J. Med. Chem.* **1999**, 42, 920). Pre-treatment of allergic sheep with a 3 mg nebulized dose of BIO-1211 (having an $\alpha 4 \beta 1$ IC₅₀ value of 1 nM; 1000-fold selective over $\alpha 4 \beta 7$) inhibited early and late airway responses following antigen challenge and prevented development of nonspecific airway hyperresponsiveness to carbachol. These results suggest that compounds like

BIO-1211 can effect broad pleiotropic activities by acting at $\alpha 4\beta 1$ to achieve pronounced efficacy similar to corticosteroids.

VLA-4 antagonism may also be effective in reducing restenosis following percutaneous coronary interventions. Administration of an anti- $\alpha 4$ antibody attenuated smooth muscle cell migration associated with electrical injury of rabbit carotid arteries (Kling D, Fingerle J, Harlan JM, Lobb, RR and Lang, F, Mononuclear leukocytes invade rabbit arterial intima during thickening formation via CD-18 and VLA-4-dependent mechanisms and stimulate smooth muscle migration, *Circ. Res.*, **1995**, 77, 1121-1128) and was shown to reduce neointimal formation in baboon carotid arteries following endarterectomy (Lumsden AB, Chen C, Hughes JD, Kelly AB, Hanson S and Harker L, Anti-VLA-4 antibody reduces intimal hyperplasia in the endarterectomized carotid artery in non-human primates, *J. Vasc. Surg.*, **1997**, 26, 87-93). Furthermore, treatment with z anti- $\alpha 4$ antibody was associated with less neoadventitia formation and less luminal narrowing 14 days after balloon injury of porcine coronary arteries (Labinez M, Hoffert C, pels K, Aggarawal S, Pepinsky RB, Leonw D, Koteliansky V, Lobb, RR and O'Brien EO, Infusion on and anti-alpha4 integrin antibody is associated with less adventitial formation after balloon injury of porcine coronary arteries, *Can. J. Cardiol.*, **2000**, 16, 187-196).

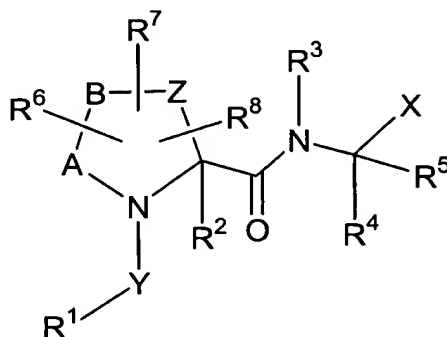
The recruitment of leukocytes, particularly monocytes to the vessel wall is a key component in the development of atherosclerotic lesions. VCAM-1 expression has been reported on endothelial cells in atherosclerotic lesions in humans (O'Brien KD, Allen MD, McDonald TO, Chait A, Harlan JM, Fishbein D, McCarty J, Ferguson M, Hudkins K, Benjamin CD, et al., Vascular cell adhesion molecule-1 is expressed in human atherosclerotic plaques: implications for the mode of progression of advanced atherosclerosis, *J. Clin. Invest.*, **1993**, 92, 945-951), mice (Nakahima Y, Raines EW, Plump AS, Breslow JL and Ross R, Upregulation of VCAM-1 and ICAM-1 at atherosclerotic-prone sites on the endothelium of ApoE-deficient mouse, *Arterioscler. Thromb. Vasc. Biol.*, **1998**, 18, 842-851) and rabbits (Ilyama K,

Hajra L, Iiyam M, Li H, DiChura M, Medoff BD and Cybulsky MI, Patterns of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 expression in rabbit and mouse atherosclerotic lesion and at sites predisposed to lesion formation, *Circ. Res.*, **1999**, 85, 199-207). Furthermore, a synthetic peptidomimetic of the connecting segment-1 (CS-1) which blocks $\alpha_4\beta_1$ on the leukocyte demonstrated reduced leukocyte homing and lipid accumulation in the aortic sinus in both wild type mice and mice with a low density lipoprotein null mutation (LDLR $-/-$) maintained on a high fat diet (Shih PT, Brennan M-L, Vora DK, Territo MC, Strahl D, Elices MJ, Aldons J and Berliner JA, Blocking very late antigen-4 integrin decreases leukocyte entry and fatty streak formation in mice fed an atherogenic diet, *Circ. Res.*, **1999**, 84, 345-351). In studies using isolated carotid arteries from ApoE $-/-$ mice (these mice develop spontaneous arterial atherosclerotic lesions with advanced lesions similar to those observed in humans), administration on blocking antibodies to VCAM-1 inhibited the majority of adhesion of monocytes or U937 cells on early atherosclerotic endothelia. In addition, a peptide which inhibits binding of $\alpha_4\beta_1$ to both VCAM-1 and fibronectin was also effective in this model (Huo Y, Hafez-Moghadem A and Ley K, Role of vascular cell adhesion molecule-1 and fibronectin connecting segment-1 in monocyte rolling and adhesion on early atherosclerotic lesions, *Circ. Res.*, **2000**, 87, 153-159). These data support the role of $\alpha_4\beta_1$ in regulating leukocyte recruitment in early and advanced atherosclerotic lesions.

Antibodies to MAdCAM-1 or integrin $\alpha_4\beta_7$ inhibit lymphocyte binding to affinity-purified MAdCAM-1 or MAdCAM-1 transfectants in vitro (Hamann, A.; et al., *J. Immunol.* **1994**, 152, 3282). The antibodies also block localization of lymphocytes to Peyer's patches. Murine MAdCAM-1 recognizes only $\alpha_4\beta_7$ positive human lymphocyte cell lines and $\alpha_4\beta_7$ -high memory T cells. An in vivo role of $\alpha_4\beta_7$ in inflammation has been suggested by increased expression of MAdCAM-1 on HEV-type vessels in the chronically inflamed pancreas of the non-obese mouse (Hanninen, A.C.; et al., *J. Clin. Invest.* **1993**, 92, 2509). In fact, animal models underscore a significant function of $\alpha_4\beta_7$ in both colitis

(Fong, S.; et al., *Immunol. Res.* **1997**, *16*, 299) and lymphocytic inflammation of pancreatic islets or development of diabetes (Yang, X.; et al., *Diabetes* **1997**, *46*, 1542).

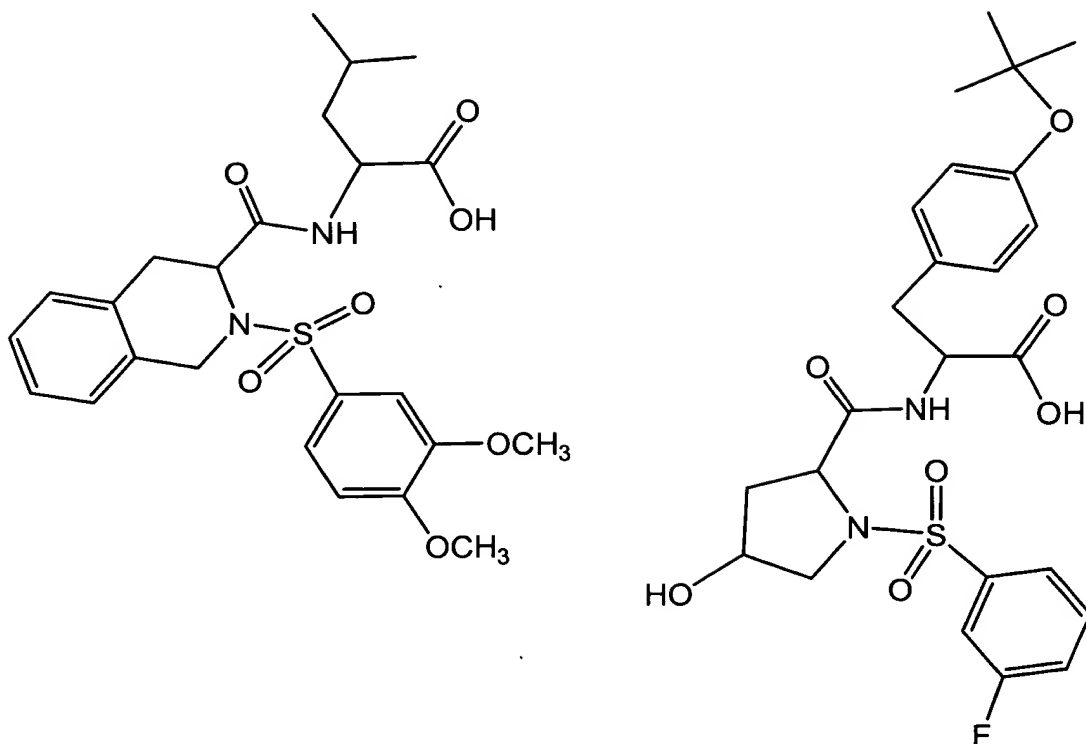
5 PCT application WO 98/53814 describes heterocyclic amide compounds as antagonists for VLA-4 and/or $\alpha 4\beta_7$ antagonists of the formula:



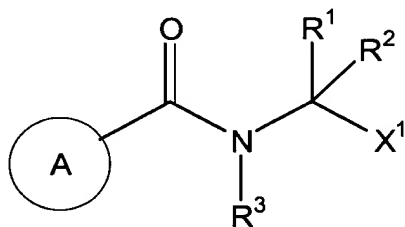
or a pharmaceutically acceptable salt thereof wherein

R¹ is alkyl, alkenyl, alkynyl, C_y, C_y-alkyl, C_y-alkenyl or C_y-alkynyl; wherein alkyl, alkenyl and alkynyl are optionally substituted with R^a; and C_y is optionally substituted with R^b; R² is hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl or heteroaralkyl; wherein alkyl, alkenyl and alkynyl are optionally substituted with R^a; and aryl and heteroaryl are optionally substituted with R^b; R³ is hydrogen, alkyl, C_y or C_y-alkyl; wherein alkyl is optionally substituted with R^a; and C_y is optionally substituted with R^b; R⁴ is hydrogen, alkyl, alkenyl, alkynyl, C_y, C_y-alkyl, C_y-alkenyl or C_y-alkynyl; wherein alkyl, alkenyl and alkynyl are optionally substituted with phenyl and R^x; and C_y is optionally substituted with R^y; or, R³, R⁴ and the atoms to which they are attached together form a mono- or bicyclic ring containing 0-2 additional heteroatoms selected from N, O and S; R⁵ is hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl or heteroaralkyl; wherein alkyl, alkenyl and alkynyl are optionally substituted with R^x; and aryl and heteroaryl are optionally substituted with R^y; or, R⁴, R⁵ and the carbon to which they are attached together form a 3-7 membered mono- or bicyclic ring containing 0-2 heteroatoms selected from N, O and S; R⁶, R⁷ and R⁸ are each independently selected from R^d or R^x; or, two of R⁶, R⁷ and R⁸ and the atom to which both are attached, or two of R⁶, R⁷ and R⁸ and the two adjacent atoms to which they are attached together form a 5-7 membered

saturated or unsaturated monocyclic ring containing 0-3 heteroatoms selected from N, O or S; R^a is C_y , or a group selected from R^x ; wherein C_y is optionally substituted with R^c ; R^b is a group selected from R^a , alkyl, alkenyl, alkynyl, aralkyl or heteroaralkyl; wherein alkyl, alkenyl, alkynyl, aryl and heteroaryl are optionally substituted with R^c ; R^b is halogen, NO_2 , $C(O)OR^f$, alkyl, alkoxy, aryl, aralkyl, aryloxy, heteroaryl, NR^fR^g , $NR^fC(O)R^g$, $NR^fC(O)NR^fR^g$, or CN; R^d and R^e are independently selected from hydrogen, alkyl, alkenyl, alkynyl, C_y and C_y -alkyl; wherein alkyl, alkenyl, alkynyl and C_y are optionally substituted with R^c ; or, R^d and R^e together with the atoms to which they are attached form a heterocyclic ring of 5-7 members containing 0-2 additional heteroatoms independently selected from N, O and S; R^f and R^g are independently selected from hydrogen, alkyl, C_y and C_y -alkyl; wherein C_y is optionally substituted with alkyl; or, R^f and R^g together with the carbon to which they are attached form a ring of 5-7 members containing 0-2 heteroatoms independently selected from N, O and S; R^h is hydrogen, alkyl, alkenyl, alkynyl, cyano, aryl, aralkyl, heteroaryl, heteroaralkyl or $-SO_2R^i$; wherein alkyl, alkenyl and alkynyl are optionally substituted with R^a ; and aryl and heteroaryl are optionally substituted with R^b ; R^i is alkyl, alkenyl, alkynyl or aryl; wherein alkyl, alkenyl, alkynyl and aryl are each optionally substituted with R^c ; R^k is $-OR^d$, $-NO_2$, halogen, $-S(O)_mR^d$, $-SR^d$, $-S(O_2)OR^d$, $-S(O)_mNR^dR^e$, $-NR^dR^e$, $-O(CR^fR^g)_nNR^dR^e$, $-C(O)R^d$, $-CO_2R^d$, $-CO_2(CR^fR^g)_nC(O)NR^dR^e$, $-OC(O)R^d$, CN, $C(O)NR^dR^e$, $-NR^dC(O)R^e$, $-OC(O)NR^dR^e$, $-NR^dC(O)OR^e$, $-NR^dC(O)NR^dR^e$, $-CR^d(N-OR^e)$, $-CF_3$, oxo, $-NR^dC(O)NR^dSO_2R^i$, $-NR^dS(O)_mR^e$, $-OS(O_2)OR^d$ or $-OP(O)(OR^d)_2$; R^y is a group selected from R^k , alkyl, alkenyl, alkynyl, aralkyl, heteroaralkyl, cycloalkyl or heterocyclyl; wherein alkyl, alkenyl, alkynyl and aryl are each optionally substituted with R^x ; C_y is cycloalkyl, heterocyclyl, aryl or heteroaryl; m is an integer from 1 to 2; n is an integer from 1 to 10; X is $-C(O)OR^d$, $-P(O)(OR^d)(OR^e)$, $-P(O)(R^d)(OR^e)$, $-S(O)_mOR^d$, $C(O)NR^dR^h$ or -5-tetrazolyl; Y is $-C(O)-$, $-O-C(O)-$, $-NR^eC(O)-$, $-SO_2-$, $-P(O)(OR^d)$ or $C(O)C(O)$; Z and A are independently selected from $-C-$ and $-C-C-$; and, B is selected from the group consisting of a bond, $-C-$, $-C-C-$, $-C=C-$, a heteroatom selected from the group consisting of N, O and S; and $-S(O)_m-$. Specific examples which exemplify some of the typical compounds disclosed have the following typical formulae:



PCT application WO 00/43354 describes multicyclic compounds as inhibitors of leukocyte adhesion mediated by VLA-4 of the formula:

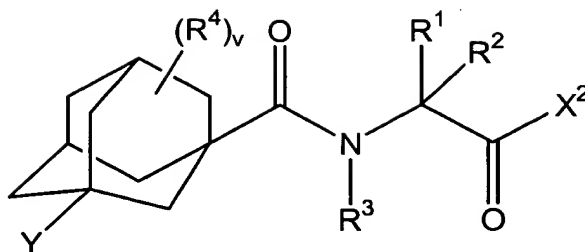


wherein ring A is a multicyclic bridged cycloalkyl, multicyclic bridged cycloalkenyl or multicyclic bridged heterocyclic group provided the multicyclic bridged heterocyclic group does not contain a lactam and further wherein said multicyclic bridged cycloalkyl, multicyclic bridged cycloalkenyl or multicyclic bridged heterocyclic group is optionally substituted, on any ring atom capable of substitution, with 1-3 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl,

substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, cyano, halogen, hydroxyl, nitro, oxo, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-\text{OS}(\text{O})_2\text{-alkyl}$, $-\text{OS}(\text{O})_2\text{-substituted alkyl}$, $-\text{OS}(\text{O})_2\text{-aryl}$, $-\text{OS}(\text{O})_2\text{-substituted aryl}$, $-\text{OS}(\text{O})_2\text{-heteroaryl}$, $-\text{OS}(\text{O})_2\text{-substituted heteroaryl}$, $-\text{OS}(\text{O})_2\text{-heterocyclic}$, $-\text{OS}(\text{O})_2\text{-substituted heterocyclic}$, $-\text{OSO}_2\text{-NRR}$ where each R is independently hydrogen or alkyl, $-\text{NRS}(\text{O})_2\text{-alkyl}$, $-\text{NRS}(\text{O})_2\text{-substituted alkyl}$, $-\text{NRS}(\text{O})_2\text{-aryl}$, $-\text{NRS}(\text{O})_2\text{-substituted aryl}$, $-\text{NRS}(\text{O})_2\text{-heteroaryl}$, $-\text{NRS}(\text{O})_2\text{-substituted heteroaryl}$, $-\text{NRS}(\text{O})_2\text{-heterocyclic}$, $-\text{NRS}(\text{O})_2\text{-substituted heterocyclic}$, $-\text{NRS}(\text{O})_2\text{-NR-alkyl}$, $-\text{NRS}(\text{O})_2\text{-NR-substituted alkyl}$, $-\text{NRS}(\text{O})_2\text{-NR-aryl}$, $-\text{NRS}(\text{O})_2\text{-NR-substituted aryl}$, $-\text{NRS}(\text{O})_2\text{-NR-heteroaryl}$, $-\text{NRS}(\text{O})_2\text{-NR-substituted heteroaryl}$, $-\text{NRS}(\text{O})_2\text{-NR-heterocyclic}$, $-\text{NRS}(\text{O})_2\text{-NR-substituted heterocyclic}$ where R is hydrogen or alkyl, $-\text{N}[\text{S}(\text{O})_2\text{-R}]_2$ And $-\text{N}[\text{S}(\text{O})_2\text{-NR}']_2$ where each R' is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and substituted alkyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkyl/substituted alkyl groups substituted with $-\text{SO}_2\text{-alkyl}$, $-\text{SO}_2\text{-substituted alkyl}$,

-SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic and -SO₂NRR where R is hydrogen or alkyl; R¹ is selected from the group consisting of: (a) -(CH₂)_x-Ar-R⁵ where R⁵ is selected from the group consisting of -O-Z-NR⁶R^{6'} and -O-Z-R⁷ wherein R⁶ and R^{6'} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R⁶ and R^{6'} are joined to form a heterocycle or a substituted heterocycle, R⁷ is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and -SO₂-, Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl, x is an integer of from 1 to 4; (b) Ar¹-Ar²-C₁₋₁₀alkyl-, Ar¹-Ar²-C₂₋₁₀alkenyl-, Ar¹-Ar²-C₂₋₁₀alkynyl-, wherein Ar¹ and Ar² are independently aryl or heteroaryl each of which is optionally substituted with one to four substituents independently selected from R^b; alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents independently selected from R^a; (c) -(CH₂)_x-Ar-R⁸, wherein R⁸ is heterocyclic or substituted heterocyclic; Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl, x is an integer of from 1 to 4; (d) -(CH₂)_x-Ar-R⁹, wherein R⁹ is -C₁₋₁₀alkyl, -C₂₋₁₀alkenyl or -C₂₋₁₀alkynyl, wherein alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents selected from R^a; Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl, x is an integer of from 1 to 4; (e) -(CH₂)_x-Cy-, wherein Cy is optionally substituted with 1 to 4 substituents selected from R² is selected from the group consisting of hydrogen, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, aryl, aryl C₁₋₁₀alkyl, heteroaryl, and heteroaryl C₁₋₁₀alkyl, wherein alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents selected from R^a, and aryl and heteroaryl are optionally substituted with one to four substituents independently selected from R^b; R³ is selected from the group consisting of hydrogen, C₁₋₁₀alkyl optionally substituted with one to four substituents independently selected from R^a and Cy optionally substituted with one to four substituents independently selected from R^b; R^a is selected from the group consisting of Cy, -OR^d, -NO₂, halogen, -S(O)_mR^d, -SR^d, -S(O)₂OR^d, -S(O)_mNR^dR^e, NR^dR^e, -O(CNR^fR^g)_nNR^dR^e, -C(O)R^d, -CO₂R^d,

$-\text{CO}_2(\text{CR}^f\text{R}^g)_n\text{CONR}^d\text{R}^e$, $-\text{OC}(\text{O})\text{R}^d$, $-\text{CN}$, $\text{C}(\text{O})\text{NR}^d\text{R}^e$, $\text{NR}^d\text{C}(\text{O})\text{R}^e$,
 $-\text{OC}(\text{O})\text{NR}^d\text{R}^e$, $-\text{NR}^d\text{C}(\text{O})\text{OR}^e$, $-\text{NR}^d\text{C}(\text{O})\text{NR}^d\text{R}^e$, $-\text{CR}^d(\text{N}-\text{OR}^e)$, CF_3 , and $-\text{OCF}_3$;
 wherein Cy is optionally substituted with one to four substituents independently
 selected from R^c ; R^b is selected from the group consisting of R^a , $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkynyl}$, aryl $\text{C}_{1-10}\text{alkyl}$, heteroaryl, $\text{C}_{1-10}\text{alkyl}$, wherein alkyl,
 alkenyl, aryl, heteroaryl are optionally substituted with a group independently
 selected from R^c ; R^c is selected from the group consisting of halogen, amino,
 carboxy, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkoxy}$, aryl, aryl $\text{C}_{1-4}\text{alkyl}$, hydroxy, CF_3 , and aryloxy; R^d
 and R^e are independently selected from hydrogen, $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkynyl}$, Cy and Cy- $\text{C}_{1-10}\text{alkyl}$, wherein alkyl, alkenyl, alkynyl and Cy are
 optionally substituted with one to four substituents independently selected from
 R^c ; or R^d and R^e together with the atoms to which they are attached form a
 heterocyclic ring of 5 to 7 members containing 0-2 additional heteroatoms
 independently selected from oxygen, sulfur and nitrogen; R^f and R^g are
 independently selected from hydrogen, $\text{C}_{1-10}\text{alkyl}$, Cy and Cy- $\text{C}_{1-10}\text{alkyl}$; or R^f and R^g together with the carbon to which they are attached form a ring of 5
 to 7 members containing 0-2 heteroatoms independently selected from
 oxygen, sulfur and nitrogen; R^h is selected from the group consisting of
 hydrogen, $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkynyl}$, cyano, aryl, aryl $\text{C}_{1-10}\text{alkyl}$,
 heteroaryl, heteroaryl $\text{C}_{1-10}\text{alkyl}$, or $-\text{SO}_2\text{R}^i$; wherein alkyl, alkenyl, and alkynyl
 are optionally substituted with one to four substituents independently selected
 from R^a ; and aryl and heteroaryl are each optionally substituted with one to four
 substituents independently selected from R^b ; R^i is selected from the group
 consisting of $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkynyl}$, and aryl; wherein alkyl,
 alkenyl, alkynyl and aryl are each optionally substituted with one to four
 substituents independently selected from R^c ; Cy is cycloalkyl, heterocyclyl, aryl,
 or heteroaryl; X^1 is selected from the group consisting of $-\text{C}(\text{O})\text{OR}^d$, $-\text{P}(\text{O})(\text{OR}^d)(\text{OR}^e)$, $-\text{P}(\text{O})(\text{R}^d)(\text{OR}^e)$, $-\text{S}(\text{O})_m\text{OR}^d$, $-\text{C}(\text{O})\text{NR}^d\text{R}^h$, and -5-tetrazolyl; m
 is an integer from 1 to 2; n is an integer from 1 to 10; and pharmaceutically
 acceptable salts thereof. Preferred compounds of this invention are
 represented by formula II:



wherein R^1 , R^2 and R^3 are as defined above; Y is selected from the group consisting of hydrogen, R^d , Cy, $-OR^d$, $-NO_2$, halogen, $-S(O)_mR^d$, $-SR^d$, $-S(O)_2OR^d$, $-S(O)_mNR^dR^e$, $-NR^dR^e$, $-O(CR^fR^g)_nNR^dR^e$, $-C(O)R^d$, $-CH(OH)R^d$, $-CO_2R^d$, $-CO_2(CR^fR^g)_nCONR^dR^e$, $-OC(O)R^d$, $-CN$, $C(O)NR^dR^e$, $NR^dC(O)R^e$, $-OC(O)NR^dR^e$, $-NR^dC(O)OR^e$, $-NR^dC(O)NR^dR^e$, $-CR^d(N-OR^e)$, CF_3 , and $-OCF_3$; wherein Cy is optionally substituted with one to four substituents independently selected from R^c ; where Cy, R^c , R^d , R^e , R^f , R^g , R^h , m and n are as defined herein; R^4 is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonyl-amino, acyloxy, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, cyano, halogen, hydroxyl, nitro, oxo, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxyllieteroaryl, carboxyl-substituted heteroaryl, carboxyllieterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thiolheteroaryl, substituted thiolheteroaryl, thiolheterocyclic, substituted thiolheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$ -alkyl, $-OS(O)_2$ -substituted alkyl, $-OS(O)_2$ -aryl, $-OS(O)_2$ -substituted aryl, $-OS(O)_2$ -heteroaryl, $-OS(O)_2$ -substituted heteroaryl, $-OS(O)_2$ -heterocyclic, $-OS(O)_2$ -substituted heterocyclic, $-OSO_2$ -NRR where each R is independently hydrogen or alkyl, $-NRS(O)_2$ -alkyl, $-NRS(O)_2$ -substituted alkyl, $-NRS(O)_2$ -aryl, $-NRS(O)_2$ -substituted aryl, $-NRS(O)_2$ -heteroaryl, $-NRS(O)_2$ -substituted heteroaryl, $-NRS(O)_2$ -heterocyclic, $-NRS(O)_2$ -

substituted heterocyclic, $\text{-NRS(O)}_2\text{-NR-alkyl}$, $\text{-NRS(O)}_2\text{-NR-substituted alkyl}$,
 $\text{-NRS(O)}_2\text{-NR-aryl}$, $\text{-NRS(O)}_2\text{-NR-substituted aryl}$, $\text{-NRS(O)}_2\text{-NR-heteroaryl}$,
 $\text{-NRS(O)}_2\text{-NR-substituted heteroaryl}$, $\text{-NRS(O)}_2\text{-NR-heterocyclic}$, $\text{-NRS(O)}_2\text{-NR-}$
substituted heterocyclic where R is hydrogen or alkyl, $\text{-N[S(O)}_2\text{-R'}]_2$ and
 $\text{-N[S(O)}_2\text{-NR'}]_2$ where each R' is independently selected from the group
consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl,
substituted heteroaryl, heterocyclic and substituted heterocyclic, mono- and di-
alkylamino, mono- and di-(substituted alkyl)amino, mono- and di- arylamino,
mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and
di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and
di-substituted heterocyclic amino, unsymmetric di-substituted amines having
different substituents selected from alkyl, substituted alkyl, aryl, substituted
aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted
heterocyclic and substituted alkyl groups having amino groups blocked by
conventional blocking groups such as Boc, Cbz, formyl, and the like or
alkyl/substituted alkyl groups substituted with $\text{-SO}_2\text{-alkyl}$, $\text{-SO}_2\text{-substituted alkyl}$,
 $\text{-SO}_2\text{-alkenyl}$, $\text{-SO}_2\text{-substituted alkenyl}$, $\text{-SO}_2\text{-cycloalkyl}$, $\text{-SO}_2\text{-substituted}$
cycloalkyl, $\text{-SO}_2\text{-aryl}$, $\text{-SO}_2\text{-substituted aryl}$, $\text{-SO}_2\text{-heteroaryl}$, $\text{-SO}_2\text{-substituted}$
heteroaryl, $\text{-SO}_2\text{-heterocyclic}$, $\text{-SO}_2\text{-substituted heterocyclic}$ and $\text{-SO}_2\text{NRR}$
where R is hydrogen or alkyl; or R^b where R^b is as defined above; X^2 is
selected from the group consisting of hydroxyl, alkoxy, substituted alkoxy,
alkenoxy, substituted alkenoxy, cycloalkoxy, substituted cycloalkoxy,
cycloalkenoxy, substituted cycloalkenoxy, aryloxy, substituted aryloxy,
heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted
heterocyclyloxy and $\text{-NR}^c\text{R}^d$ where each R^c is independently selected from the
group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted
alkenyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl,
substituted heteroaryl, heterocyclic and substituted heterocyclic; or R^d where
 R^d is as defined above; v is an integer ranging from 0 to 3; and
pharmaceutically acceptable salts thereof.

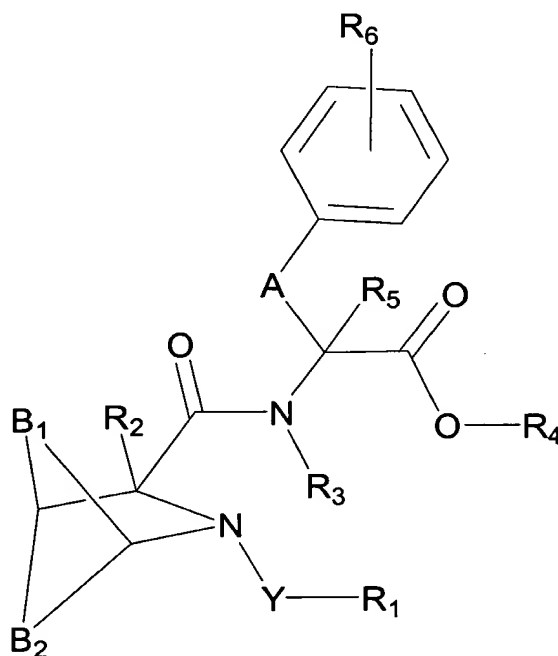
The structural topology represented by the formulae described in these references differs significantly from that represented by the compounds of the

present invention.

Accordingly, it is an object of the present invention to provide aza-bridged-bicyclic compounds that are α_4 integrin receptor antagonists; more particularly, the $\alpha_4\beta_1$ and the $\alpha_4\beta_7$ integrin receptor. It is also an object of the present invention to provide a process for preparing derivatives of aza-bridged-bicyclic amino acid compounds, compositions, intermediates and derivatives thereof. It is a further object of the invention to provide methods for the treatment of integrin mediated disorders that are ameliorated by inhibition of the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin receptor including, but not limited to, inflammatory, autoimmune and cell-proliferative disorders.

Summary of the Invention

The present invention is directed to aza-bridged-bicyclic compounds having Formula (I):



Formula (I)

wherein

Y is selected from the group consisting of a bond, -C(O)-, -C(O)O-, -C(O)NH- and -SO₂-;

R₁ is selected from the group consisting of R₇ and R₈;

R₂, R₃, R₄ and R₅ are independently selected from the group consisting of a bond, hydrogen and C₁₋₈alkyl; wherein C₁₋₈alkyl is optionally substituted with one to three substituents independently selected from R₉, provided that R₂, R₃, R₄ or R₅ can only be a bond when forming a monocyclic ring wherein the following monocyclic rings may be formed from R₂, R₃, R₄ and R₅;

when R₂ and R₃ comprise a bond and C₁₋₈alkyl or optionally when both R₂ and R₃ are C₁₋₈alkyl, R₂ and R₃ together with the atoms to which each is attached will form a four to seven membered monocyclic ring optionally containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

when R₃ and R₄ comprise a bond and C₁₋₈alkyl or optionally when both R₃ and R₄ are C₁₋₈alkyl, R₃ and R₄ together with the atoms to which each is attached will form a five to seven membered monocyclic ring optionally containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

when R₃ and R₅ comprise a bond and C₁₋₈alkyl or optionally when both R₃ and R₅ are C₁₋₈alkyl, R₃ and R₅ together with the atoms to which each is attached will form a four to seven membered monocyclic ring optionally containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

when R₄ and R₅ comprise a bond and C₁₋₈alkyl, or optionally when both R₄ and R₅ are C₁₋₈alkyl, R₄ and R₅ together with the atoms to which each is attached will form a four to seven membered monocyclic ring optionally containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

R_6 is optionally present and is one to three substituents independently selected from the group consisting of halogen, C_{1-8} alkoxy, R_{10} , R_{12} , $-N(R_{11})C(O)-R_{10}$, $-N(R_{11})C(O)-R_{12}$, $-N(R_{11})SO_2-R_{10}$, $-N(R_{11})SO_2-R_{12}$, $-N(R_{11})C(O)-N(R_{11},R_{10})$, $-N(R_{11})C(O)-N(R_{11},R_{12})$, $-N(R_{11})C(O)-N(R_{12},R_{17})$, $-C(O)-N(R_{11},R_{10})$, $-C(O)-N(R_{11},R_{12})$, $-C(O)-N(R_{12},R_{17})$, $-OC(O)-N(R_{11},R_{10})$, $-OC(O)-N(R_{11},R_{12})$, $-OC(O)-N(R_{12},R_{17})$, $-OC(O)-R_{10}$, $-OC(O)-R_{12}$, $-O-R_{10}$ and $R_{10}-(C_{1-8})$ alkoxy;

R_7 , R_9 , R_{10} and R_{14} are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl optionally substituted with one to five substituents independently selected from the group consisting of halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkylcarbonyl, C_{1-8} alkoxycarbonyl, carboxyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, arylsulfonyl, amino, $N-(C_{1-8})$ alkylamino, $N,N-(C_{1-8})$ dialkylamino, $-CF_3$ and $-OCF_3$; wherein cycloalkyl and heterocyclyl are optionally substituted with one to three oxo substituents; and, wherein the aryl and heteroaryl substituents and the aryl portion of the arylcarbonyl substituent are optionally substituted with one to five substituents independently selected from the group consisting of halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, carboxyl, amino, $N-(C_{1-8})$ alkylamino, $N,N-(C_{1-8})$ dialkylamino, $-CF_3$ and $-OCF_3$;

R_8 , R_{12} , R_{13} and R_{17} are independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, and $(halo)_{1-3}(C_{1-8})$ alkyl; wherein C_{1-8} alkyl, C_{2-8} alkenyl and C_{2-8} alkynyl are optionally substituted on a terminal carbon with one to three substituents independently selected from R_{14} ;

R_{11} is selected from the group consisting of hydrogen and C_{1-8} alkyl;

A is C_{1-4} alkylene optionally substituted with one to two substituents independently selected from R_{13} ;

when R_3 is C_{1-8} alkyl, optionally A and R_3 together with the atoms to which each is attached may form a five to seven membered monocyclic ring optionally

containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

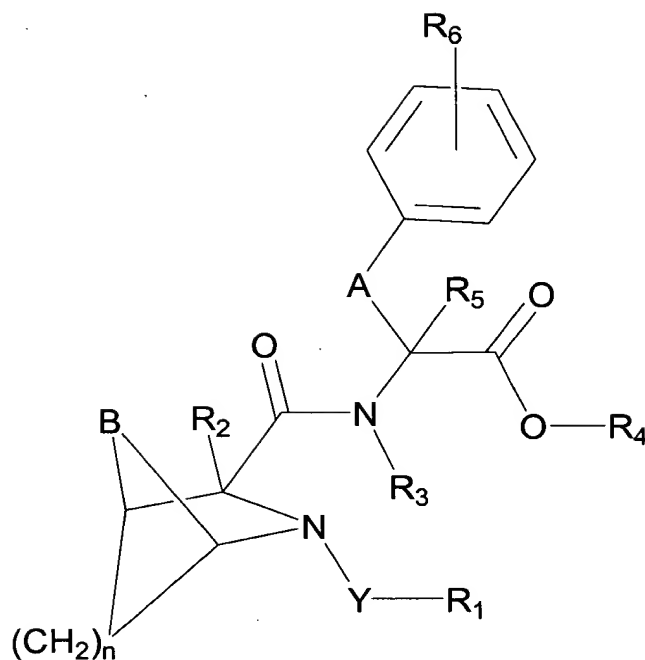
when R_4 is C_{1-8} alkyl, optionally A and R_4 together with the atoms which each is attached may form a five to seven membered monocyclic ring optionally containing one additional heteroatom selected from the group consisting of N, O and S;

when R_5 is C_{1-8} alkyl, optionally A and R_5 together with the atoms which each is attached may form a three to seven membered monocyclic ring optionally containing one to two heteroatoms independently selected from the group consisting of N, O and S; and,

B_1 and B_2 are independently selected from the group consisting of C_{1-8} alkylene and C_{2-8} alkenylene optionally substituted with one to two substituents independently selected from the group consisting of halogen, hydroxy, hydroxy(C_{1-8})alkyl, hydroxy(C_{1-8})alkoxy, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, carboxyl, amino, *N*-(C_{1-8} alkyl)amino, *N,N*-(C_{1-8} dialkyl)amino, $-CF_3$ and $-OCF_3$;

and pharmaceutically acceptable salts, racemic mixtures, diastereomers and enantiomers thereof.

An embodiment of the present invention is directed to aza-bridged-bicyclic compounds having Formula (II):



Formula (II)

wherein

Y is selected from the group consisting of -C(O)- and -SO₂-;

R₁ is selected from the group consisting of R₇ and R₈;

R₂, R₃, R₄ and R₅ are independently selected from the group consisting of a bond, hydrogen and C₁₋₈alkyl; wherein C₁₋₈alkyl is optionally substituted with one to three substituents independently selected from R₉; provided that R₂, R₃, R₄ and R₅ can only be a bond when forming a monocyclic ring wherein the following monocyclic rings may be formed from R₂, R₃, R₄ and R₅:

when R₂ and R₃ comprise a bond and C₁₋₈alkyl or optionally when both R₂ and R₃ are C₁₋₈alkyl, R₂ and R₃ together with the atoms to which each are attached form a four to seven membered monocyclic ring optionally containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

when R₃ and R₄ comprise a bond and C₁₋₈alkyl or optionally when both R₃ and R₄ are C₁₋₈alkyl, R₃ and R₄ together with the atoms to which each are attached form a five to seven membered monocyclic ring optionally

containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

when R_3 and R_5 comprise a bond and C_{1-8} alkyl or optionally when both R_3 and R_5 are C_{1-8} alkyl, R_3 and R_5 together with the atoms to which each are attached form a four to seven membered monocyclic ring optionally containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

when R_4 and R_5 comprise a bond and C_{1-8} alkyl or optionally when both R_4 and R_5 are C_{1-8} alkyl, R_4 and R_5 together with the atoms to which each are attached form a four to seven membered monocyclic ring optionally containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

R_6 is optionally present and is one to three substituents independently selected from the group consisting of halogen, C_{1-8} alkoxy, R_{10} , R_{12} , $-N(R_{11})C(O)-R_{10}$, $-N(R_{11})C(O)-R_{12}$, $-N(R_{11})SO_2-R_{10}$, $-N(R_{11})SO_2-R_{12}$, $-N(R_{11})C(O)-N(R_{11},R_{10})$, $-N(R_{11})C(O)-N(R_{11},R_{12})$, $-N(R_{11})C(O)-N(R_{12},R_{17})$, $-C(O)-N(R_{11},R_{10})$, $-C(O)-N(R_{11},R_{12})$, $-C(O)-N(R_{12},R_{17})$, $-OC(O)-N(R_{11},R_{10})$, $-OC(O)-N(R_{11},R_{12})$, $-OC(O)-N(R_{12},R_{17})$, $-OC(O)-R_{10}$, $-OC(O)-R_{12}$, $-O-R_{10}$ and $R_{10}-(C_{1-8})alkoxy$;

R_7 , R_9 , R_{10} and R_{14} are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl optionally substituted with one to five substituents independently selected from the group consisting of halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkylcarbonyl, C_{1-8} alkoxycarbonyl, carboxyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, arylsulfonyl, amino, $N-(C_{1-8}alkyl)amino$, $N,N-(C_{1-8}dialkyl)amino$, $-CF_3$ and $-OCF_3$; wherein cycloalkyl and heterocyclyl are optionally substituted with one to three oxo substituents; and, wherein the aryl and heteroaryl substituents and the aryl portion of the arylcarbonyl substituent are optionally substituted with one to five substituents independently selected from the group consisting of halogen, C_{1-8} alkyl,

C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, carboxyl, amino, N -(C_{1-8} alkyl)amino, N,N -(C_{1-8} dialkyl)amino, $-CF_3$ and $-OCF_3$;

R_8 , R_{12} , R_{13} and R_{17} are independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, and (halo) $_{1-3}$ (C_{1-8})alkyl; wherein C_{1-8} alkyl, C_{2-8} alkenyl and C_{2-8} alkynyl are optionally substituted on a terminal carbon with one to three substituents independently selected from R_{14} ;

R_{11} is selected from the group consisting of hydrogen and C_{1-8} alkyl;

A is C_{1-4} alkylene optionally substituted with one to two substituents independently selected from R_{13} ;

when R_3 is C_{1-8} alkyl, optionally A and R_3 together with the atoms to which each is attached form a five to seven membered monocyclic ring optionally containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

when R_4 is C_{1-8} alkyl, optionally A and R_4 together with the atoms to which each is attached form a five to seven membered monocyclic ring optionally containing one additional heteroatom selected from the group consisting of N, O and S;

when R_5 is C_{1-8} alkyl, optionally A and R_3 together with the atoms to which each is attached form a three to seven membered monocyclic ring optionally containing one to two heteroatoms independently selected from the group consisting of N, O and S;

B is selected from the group consisting of C_{1-8} alkylene and C_{2-8} alkenylene optionally substituted with one to two substituents independently selected from the group consisting of halogen, hydroxy, hydroxy(C_{1-8})alkyl, hydroxy(C_{1-8})alkoxy, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, carboxyl, amino, N -(C_{1-8} alkyl)amino, N,N -(C_{1-8} dialkyl)amino, $-CF_3$ and $-OCF_3$; and,

n is an integer from 1 to 2;

and pharmaceutically acceptable salts, racemic mixtures, diastereomers and enantiomers thereof.

An embodiment of the present invention is also directed to a process for preparing the instant aza-bridged-bicyclic compounds, compositions, intermediates and derivatives thereof. Another embodiment of the present invention is directed to pharmaceutical compositions comprising the compounds of the present invention.

The aza-bridged-bicyclic amino acid derivatives of the present invention are useful α_4 integrin receptor antagonists and, more particularly, $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin receptor antagonists. A further embodiment of the present invention is directed to a method for the treatment of integrin mediated disorders that are ameliorated by inhibition of the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin receptor including, but not limited to, inflammatory, autoimmune and cell-proliferative disorders. In an illustration of the invention, the inflammatory, autoimmune and cell-proliferative disorders include, but are not limited to, inflammation and autoimmunity, asthma and bronchoconstriction, restenosis and atherosclerosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, transplant rejection and multiple sclerosis.

Detailed Description of the Invention

We have discovered that the position and type of the substituents on the phenyl group of the phenylalanine amino acid, in combination with stereochemistry, have a significant effect on the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin receptor antagonist activity of the aza-bridged-bicyclic compounds of the present invention. Relative to the above generic description, certain compounds having Formula (I) are preferred.

The preferred embodiments of the aza-bridged-bicyclic compounds of the present invention include those compounds wherein the phenyl group of the phenylalanine amino acid is substituted on the *para* position with R₆. Further disclosed herein are experimental results demonstrating that the activity of certain aza-bridged-bicyclic compounds of the present invention as $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin receptor antagonists decreases significantly when the phenyl group of the phenylalanine amino acid is substituted on the *meta* position with R₆.

Preferred embodiments of the instant compounds also include those aza-bridged-bicyclic compounds wherein R₆ is benzofused heterocyclyl, aryl, arylamido, heteroaryl, ureido (wherein the terminal amino is dialkyl substituted), aminocarbonyloxy (wherein amino is dialkyl substituted) and aryl(C₁₋₈)alkoxy. Experimental results seem to demonstrate that the activity of certain compounds as $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin receptor antagonists increases significantly when the aryl and heteroaryl portion of R₆ is further mono- or di-substituted at the *ortho* position.

In addition to the above discoveries relative to the structure of the compounds of the present invention, we have experimentally determined that the stereochemistry significantly affects the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin receptor antagonist activity of certain compounds. In addition to racemic mixtures demonstrating activity as $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin receptor antagonists, experimental results have shown that individual diastereomers each have either a significantly increased or significantly decreased activity as an $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin receptor antagonist.

For example, Table I compares the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin receptor antagonist activity as a value of IC₅₀ for the racemic mixtures and resolved (S,S) and (R,S) diastereomers.

Table I
Antagonist IC₅₀ Activity (nM)

| Racemic Mixture | | | (S,S) diastereomer | | | (R,S) diastereomer | | |
|-----------------|-------------------|-------------------|--------------------|-------------------|-------------------|--------------------|-------------------|-------------------|
| Cpd | Activity | | Cpd | Activity | | Cpd | Activity | |
| | $\alpha_4\beta_1$ | $\alpha_4\beta_7$ | | $\alpha_4\beta_1$ | $\alpha_4\beta_7$ | | $\alpha_4\beta_1$ | $\alpha_4\beta_7$ |
| 6 | 20 | 283 | 5a | 81 | 62 | 5b | 394 | 3380 |
| | | | 6a | 23 | 217 | 6b | 222 | 421 |
| | | | 16a | 153 | 2090 | 16b | 240 | 393 |
| 18 | 124 | 210 | 18a | 857 | 9000 | 19b | 1210 | 3220 |
| | | | 19a | 300 | 3822 | | | |
| | | | 47a | 26 | 102 | | | |
| 47 | 74 | 83 | 47a | 26 | 102 | 19b | 1210 | 3220 |
| 52 | 124 | 998 | 52a | 45 | 436 | | | |
| 53 | 179 | 871 | 53a | 219 | 693 | | | |
| 71 | 9 | 30 | 71a | 6 | 33 | | | |
| | | | | | | | | |

Although the racemic mixtures have significant activity compared to the resolved diastereomers, the (S,S) diastereomers appear to generally have higher activity than the (R,S) diastereomers. The scope of the present invention is intended to encompass all racemic mixtures, enantiomers and diastereomers including, but not limited to, (R/S,S), (R/S,R), (S,R/S), (R,R/S), (S,S), (R,S), (S,R) and (R,R) diastereomers and enantiomers of the compounds of the present invention without limitation.

Preferred embodiments are those aza-bridged-bicyclic compounds wherein Y is selected from the group consisting of -C(O)- and -SO₂-. More preferably, Y is selected from -SO₂-.

Preferred embodiments include those compounds wherein R₁ is selected from R₇. R₇ is preferably selected from the group consisting of aryl and heteroaryl optionally substituted with one to five substituents independently selected from the group consisting of halogen, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₁₋₈alkoxy, C₁₋₈alkylcarbonyl, C₁₋₈alkoxycarbonyl, carboxyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, arylsulfonyl, amino, N-(C₁₋₈alkyl)amino, N,N-(C₁₋₈dialkyl)amino, -CF₃ and -OCF₃; and, wherein the

aryl and heteroaryl substituents and the aryl portion of the arylcarbonyl substituent are optionally substituted with one to five substituents independently selected from the group consisting of halogen, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₁₋₈alkoxy, carboxyl, amino, N-(C₁₋₈alkyl)amino, N,N-(C₁₋₈dialkyl)amino, -CF₃ and -OCF₃. Most preferred embodiments include those compounds wherein R₇ is selected from the group consisting of tolyl, phenyl and thienyl.

Preferred embodiments include those compounds wherein R₂, R₃, R₄ and R₅ are independently selected from the group consisting of hydrogen and C₁₋₄alkyl. More preferably, R₂, R₃, R₄ and R₅ are independently selected from the group consisting of hydrogen and methyl.

Preferred embodiments include those compounds wherein R₆ is optionally present and is one to three substituents independently selected from the group consisting of halogen, C₁₋₈alkoxy, R₁₀, R₁₂, -N(R₁₁)C(O)-R₁₀, -N(R₁₁)C(O)-R₁₂, -N(R₁₁)SO₂-R₁₀, -N(R₁₁)C(O)-N(R₁₁,R₁₂), -N(R₁₁)C(O)-N(R₁₂,R₁₇), -OC(O)-N(R₁₁,R₁₂), -OC(O)-N(R₁₂,R₁₇), -OC(O)-R₁₀ and R₁₀-(C₁₋₈)alkoxy. More preferably, R₆ is optionally present and is one to three substituents independently selected from the group consisting of halogen, C₁₋₄alkoxy, R₁₀, R₁₂, -N(R₁₁)C(O)-R₁₀, -N(R₁₁)C(O)-R₁₂, -N(R₁₁)SO₂-R₁₀, -N(R₁₁)C(O)-N(R₁₁,R₁₂), -N(R₁₁)C(O)-N(R₁₂,R₁₇), -OC(O)-N(R₁₁,R₁₂), -OC(O)-N(R₁₂,R₁₇), -OC(O)-R₁₀ and R₁₀-(C₁₋₄)alkoxy. Most preferably, R₆ is one substituent selected from the group consisting of R₁₀, -N(R₁₁)C(O)-R₁₀, -N(R₁₁)C(O)-N(R₁₁,R₁₂), -N(R₁₁)C(O)-N(R₁₂,R₁₇), -OC(O)-N(R₁₁,R₁₂), -OC(O)-N(R₁₂,R₁₇), -OC(O)-R₁₀ and R₁₀-methoxy.

Preferred embodiments include those compounds wherein R₁₀ is selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl optionally substituted with one to five substituents independently selected from the group consisting of halogen, C₁₋₈alkyl, C₁₋₈alkoxy, C₁₋₈alkoxycarbonyl, carboxyl, arylcarbonyl, arylsulfonyl, -CF₃ and -OCF₃; wherein cycloalkyl and heterocyclyl are optionally substituted with one to three

oxo substituents ; and, wherein the aryl portion of the arylcarbonyl substituent is optionally substituted with one to five substituents independently selected from C₁₋₈alkoxy.

5 More preferably R₁₀ is selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl optionally substituted with one to five substituents independently selected from the group consisting of halogen, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxycarbonyl, carboxyl, arylcarbonyl, arylsulfonyl, -CF₃ and -OCF₃; wherein cycloalkyl and heterocyclyl are optionally substituted
10 with one to three oxo substituents ; and, wherein the aryl portion of the arylcarbonyl substituent is optionally substituted with one to five substituents independently selected from C₁₋₄alkoxy.

15 Most preferably R₁₀ is selected from the group consisting of cyclopropyl, 1,3-dihydro-2*H*-isoindolyl, 2-azabicyclo[2.2.2]octyl, piperidinyl, morpholinyl, phenyl, naphthalenyl, thienyl, 1*H*-pyrrolyl and pyridinyl; wherein cyclopropyl, piperidinyl, morpholinyl, phenyl, naphthalenyl, thienyl, 1*H*-pyrrolyl and pyridinyl
20 are optionally substituted with one to four substituents independently selected from the group consisting of chlorine, fluorine, bromine, methyl, isopropyl, *t*-butyl, methoxy, *t*-butoxycarbonyl, carboxyl, phenylcarbonyl (wherein the phenyl portion of phenylcarbonyl is optionally substituted with one to two substituents selected from methoxy), -CF₃ and -OCF₃; wherein 1,3-dihydro-2*H*-isoindolyl is optionally substituted with oxo; and, wherein 2-azabicyclo[2.2.2]octyl is optionally substituted with phenylsulfonyl.

25 Preferred embodiments include those compounds wherein R₁₂ is selected from the group consisting of C₁₋₈alkyl and C₂₋₈alkynyl optionally substituted on a terminal carbon with R₁₄. More preferably, R₁₂ is selected from the group consisting of C₁₋₄alkyl and C₂₋₄alkynyl optionally substituted on a
30 terminal carbon with R₁₄. Most preferably, R₁₂ is selected from the group consisting of *t*-butyl and ethynyl; wherein ethynyl is optionally substituted on a terminal carbon with a substituent R₁₄.

Preferred embodiments include those compounds wherein R_{14} is preferably aryl optionally substituted with one to five substituents independently selected from the group consisting of halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkylcarbonyl, C_{1-8} alkoxycarbonyl, carboxyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, arylsulfonyl, amino, N -(C_{1-8} alkyl)amino, N,N -(C_{1-8} dialkyl)amino, $-CF_3$ and $-OCF_3$; and, wherein the aryl and heteroaryl substituents and the aryl portion of the arylcarbonyl substituent are optionally substituted with one to five substituents independently selected from the group consisting of halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, carboxyl, amino, N -(C_{1-8} alkyl)amino, N,N -(C_{1-8} dialkyl)amino, $-CF_3$ and $-OCF_3$. Most preferably R_{14} is most preferably is selected from the group consisting of phenyl and C_{1-8} alkylphenyl.

Preferred embodiments include those compounds wherein R_{11} is selected from the group consisting of hydrogen and C_{1-4} alkyl. More preferably, R_{11} is hydrogen.

Preferred embodiments include those compounds wherein A is selected from the group consisting of methylene and ethylene. Most preferably A is methylene.

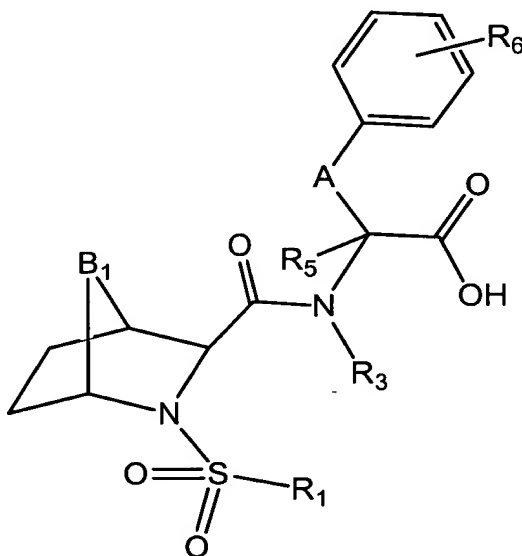
Preferred embodiments include those compounds wherein B_1 and B_2 are independently selected from the group consisting of C_{1-4} alkylene and C_{2-4} alkenylene optionally substituted with one to two substituents independently selected from the group consisting of halogen, hydroxy, hydroxy(C_{1-4})alkyl, hydroxy(C_{1-4})alkoxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, carboxyl, amino, N -(C_{1-4} alkyl)amino, N,N -(C_{1-4} dialkyl)amino, $-CF_3$ and $-OCF_3$.

More preferably, B_1 and B_2 are independently selected from the group consisting of $-CH_2-$, $-(CH_2)_2-$ and $-(CH)_2-$ optionally substituted with one to two substituents independently selected from the group consisting of halogen, hydroxy, hydroxy(C_{1-4})alkyl, hydroxy(C_{1-4})alkoxy, C_{1-4} alkyl, C_{2-4} alkenyl,

C₂₋₄alkynyl, C₁₋₄alkoxy, carboxyl, amino, *N*-(C₁₋₄alkyl)amino, *N,N*-(C₁₋₄dialkyl)amino, -CF₃ and -OCF₃. Also more preferably, B₁ is selected from the group consisting of -CH₂-, -(CH₂)₂- and -(CH)₂- optionally substituted with one to two substituents independently selected from the group consisting of halogen, hydroxy, hydroxy(C₁₋₄)alkyl, hydroxy(C₁₋₄)alkoxy, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, carboxyl, amino, *N*-(C₁₋₄alkyl)amino, *N,N*-(C₁₋₄dialkyl)amino, -CF₃ and -OCF₃ and that B₂ is selected from -(CH₂)₂-. Most preferably, B₁ is selected from the group consisting of -CH₂-, -(CH₂)₂- and -(CH)₂-.

Embodiments of the aza-bridged-bicyclic amino acid compounds of the present invention include those compounds of Formula (I) shown in Table II of the formula:

TABLE II



wherein B₁, R₁, R₃, R₅, A and R₆ are dependently selected from the group consisting of:

| Cpd | B ₁ | R ₁ | R ₃ | R ₅ | A | R ₆ |
|-------|---------------------------------|----------------|----------------|----------------|-----------------|--------------------------------------|
| 1 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-NHC(O)-(2,6-Cl ₂)Ph |
| 2 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-NHC(O)-(2,4,6-Cl ₃)Ph |
| 3 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-NHC(O)-[2,6-(OMe) ₂]Ph |
| 5a/5b | CH ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-(2,6-F ₂)Ph |

| | | | | | | |
|----------------|---------------------------------|-------|-----------------|-----------------|-----------------|--|
| 6/6a/6b | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-(2,6-Cl ₂)Ph |
| 8 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-[2,6-(OMe) ₂]Ph |
| 9 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-NHC(O)-(2-Me)Ph |
| 10 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-NHC(O)-(2-Cl)Ph |
| 11 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-NHC(O)-(2,6-F ₂)Ph |
| 12 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-NHC(O)-(2-CF ₃)Ph |
| 13 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-NHC(O)-(2-OCF ₃)Ph |
| 14 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-NHC(O)-(2-Br)Ph |
| 15 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-(2,6-F ₂)Ph |
| 16a/16b | CH ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-(2,6-Cl ₂)Ph |
| 18/18a | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-[2,6-(OMe) ₂]Ph |
| 19a/19b | CH ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-[2,6-(OMe) ₂]Ph |
| 23 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-CC-(4- <i>t</i> -butyl)Ph |
| 24 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-CC-Ph |
| 25 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-NHC(O)-Ph |
| 26 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-NHC(O)-[4-C(O)-[2,5-(OMe) ₂]Ph]Ph |
| 27 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-NHC(O)-CH ₂ -(2,6-Cl ₂)Ph |
| 28 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-NH-(2,6-Cl ₂)Ph |
| 29 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-OCH ₂ -(2,6-Cl ₂)Ph |
| 30 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-OCH ₂ -Ph |
| 31 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-NHC(O)-(2,4,6-isopropyl ₃)Ph |
| 32 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-(1 <i>H</i> -pyrrol-1-yl) |
| 33 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 4-Ph |
| 34 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-NH-(2,6-F ₂)Ph |
| 35 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 3-NHC(O)-(2,6-F ₂)Ph |
| 36 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 3-NHC(O)-[2,6-(OMe) ₂]Ph |
| 37 | (CH ₂) ₂ | 4-Tol | H | H | CH ₂ | 3-NHC(O)-(2,6-Cl ₂)Ph |
| 38 | (CH ₂) ₂ | Ph | H | CH ₃ | CH ₂ | 4-OCH ₂ -(2,6-Cl ₂)Ph |
| 39 | (CH ₂) ₂ | Ph | CH ₃ | H | CH ₂ | 4-NHC(O)-(2,6-Cl ₂)Ph |
| 40 | (CH) ₂ | Ph | H | H | CH ₂ | 4-OCH ₂ -(2,6-Cl ₂)Ph |
| 41 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-OCH ₂ -(2,6-Cl ₂)Ph |
| 42 | (CH) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-(2,6-Cl ₂)Ph |
| 43 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-(2,4,6-F ₃)Ph |

| | | | | | | |
|---------|---------------------------------|-------|---|---|---------------------------------|---|
| 44 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-(2,3,5,6-F ₄)Ph |
| 45 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-O- <i>t</i> -butoxy |
| 46 | (CH ₂) ₂ | Ph | H | H | (CH ₂) ₂ | --- |
| 47/47a | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-(1,3-dihydro-1,3-dioxo-2 <i>H</i> -isoindol-2-yl) |
| 48 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-(2-CO ₂ H)Ph |
| 49 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-(2,5-diMe-1 <i>H</i> -pyrrol-1-yl) |
| 50/50a | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-4-pyridinyl |
| 51 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHSO ₂ -(2,6-Cl ₂)Ph |
| 52/52a | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-OC(O)-N(CH ₃) ₂ |
| 53/53a | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-(1- <i>t</i> -butoxycarbonyl)4-piperidinyl |
| 54 | (CH ₂) ₂ | 4-FPh | H | H | CH ₂ | 4-NHC(O)-(2,6-Cl ₂)Ph |
| 55 | (CH ₂) ₂ | 4-FPh | H | H | CH ₂ | 4-NHC(O)-[2,6-(OMe) ₂]Ph |
| 56 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-OC(O)-4-morpholinyl |
| 57 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-OC(O)N(<i>iso</i> -propyl) ₂ |
| 58 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4- <i>t</i> -butyl |
| 59 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-4-piperidinyl |
| 60 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-(3,5-Cl ₂)4-pyridinyl |
| 61 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-NMe ₂ |
| 62a-62d | (CH ₂) ₂ | Ph | H | H | CH ₂ | 3-F-4-[OCH ₂ (2,6-Cl ₂)Ph] |
| 63 | (CH ₂) ₂ | 2-Thi | H | H | CH ₂ | 4-OC(O)-NMe ₂ |
| 64 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)- <i>t</i> -butyl |
| 65 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-(2-OMe)1-naphthalenyl |
| 66 | (CH ₂) ₂ | 2-Thi | H | H | CH ₂ | 4-NHC(O)-(2,6-Cl ₂)Ph |
| 67 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-cyclopropyl |
| 68 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-(2,2,3,3-Me ₄)cyclopropyl |
| 69 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)- <i>iso</i> -propyl |
| 70 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-(2-SO ₂ Ph)-2-azabicyclo[2.2.2]oct-3-yl |
| 71/71a | (CH ₂) ₂ | 2-Thi | H | H | CH ₂ | 4-NHC(O)-(3,5-Cl ₂)4-pyridinyl |
| 72 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-NHC(O)-(2- |

| | | | | | | |
|----|---------------------------------|-------|---|---|-----------------|--|
| | | | | | | Me)cyclopropyl |
| 73 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-(2,6-diMe)Ph |
| 74 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-(2,6-Cl ₂)Ph |
| 75 | (CH ₂) ₂ | 2-Thi | H | H | CH ₂ | 4-(2,6-Cl ₂)Ph |
| 76 | (CH ₂) ₂ | 2-Thi | H | H | CH ₂ | 4-(2,6-diMe)Ph |
| 77 | (CH ₂) ₂ | 2-Thi | H | H | CH ₂ | 4-[2,6-(OMe) ₂]Ph |
| 78 | (CH ₂) ₂ | 2-Thi | H | H | CH ₂ | 4-(4-fluoro-1,3-dihydro-1,3-dioxo-2 <i>H</i> -isoindol-2-yl) |
| 79 | (CH ₂) ₂ | 2-Thi | H | H | CH ₂ | 4-NHC(O)-NMe ₂ |
| 80 | (CH ₂) ₂ | 2-Thi | H | H | CH ₂ | 4-OC(O)-NMe ₂ |
| 81 | (CH ₂) ₂ | 2-Thi | H | H | CH ₂ | 4-OC(O)-(4-morpholinyl) |
| 82 | (CH ₂) ₂ | 2-Thi | H | H | CH ₂ | 4-OC(O)-(4-Me-1-piperazinyl) |
| 83 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-OC(O)-(4-Me-1-piperazinyl) |
| 84 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-N(Me)C(O)-(2,6-Cl ₂)Ph |
| 85 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-N(Me)C(O)-(3,5-Cl ₂)4-pyridinyl |
| 86 | (CH ₂) ₂ | 2-Thi | H | H | CH ₂ | 4-N(Me)C(O)-(3,5-Cl ₂)4-pyridinyl |
| 87 | (CH ₂) ₂ | 2-Thi | H | H | CH ₂ | 4-N(Me)C(O)-(2,6-Cl ₂)Ph |
| 88 | (CH ₂) ₂ | 2-Thi | H | H | CH ₂ | 4-OCH ₂ -(2,6-Cl ₂)Ph |
| 89 | (CH ₂) ₂ | 2-Thi | H | H | CH ₂ | 4-(1,3-dihydro-1,3-dioxo-2 <i>H</i> -isoindol-2-yl) |
| 90 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-(1,3-dihydro-4,7-dimethyl-1,3-dioxo-2 <i>H</i> -isoindol-2-yl) |
| 91 | (CH ₂) ₂ | 2-Thi | H | H | CH ₂ | 4-(1,3-dihydro-4,7-dimethyl-1,3-dioxo-2 <i>H</i> -isoindol-2-yl) |
| 92 | CH ₂ | 2-Thi | H | H | CH ₂ | 4-NHC(O)-(3,5-Cl ₂)4-pyridinyl |
| 93 | CH ₂ | 2-Thi | H | H | CH ₂ | 4-NHC(O)-(2,6-Cl ₂)Ph |
| 94 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3 <i>H</i>)-yl) |
| 95 | (CH ₂) ₂ | Ph | H | H | CH ₂ | 4-(4-chloro-1,3-dihydro-1,3-dioxo-2 <i>H</i> - |

isoindol-2-yl)

and,

96 $(\text{CH}_2)_2$

Ph

H

H

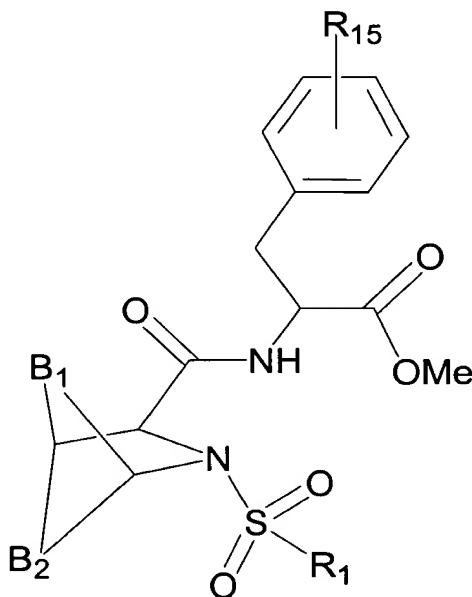
 CH_2

4-(7,9-dioxo-8-azaspiro[4.5]dec-8-yl)

and pharmaceutically acceptable salts, racemic mixtures, diastereomers and enantiomers thereof.

5

An embodiment of the present invention is a process for preparing an intermediate compound of Formula (III)



Formula (III)

wherein

R_1 is selected from the group consisting of R_7 and R_8 ;

10

R_7 , R_{10} and R_{14} are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl optionally substituted with one to five substituents independently selected from the group consisting of halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkylcarbonyl, C_{1-8} alkoxycarbonyl, carboxyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, arylsulfonyl, amino, N -(C_{1-8} alkyl)amino,

15

N,N -(C_{1-8} dialkyl)amino, $-\text{CF}_3$ and $-\text{OCF}_3$; wherein cycloalkyl and heterocyclyl are optionally substituted with one to three substituents independently

selected from oxo; and, wherein the aryl and heteroaryl substituents and the aryl portion of the arylcarbonyl substituent are optionally substituted with one to five substituents independently selected from the group consisting of halogen, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₁₋₈alkoxy, carboxyl, amino, *N*-(C₁₋₈alkyl)amino, *N,N*-(C₁₋₈dialkyl)amino, -CF₃ and -OCF₃;

R₈, R₁₂ and R₁₇ are independently selected from the group consisting of C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, and (halo)₁₋₃(C₁₋₈)alkyl; wherein C₁₋₈alkyl, C₂₋₈alkenyl and C₂₋₈alkynyl are optionally substituted on a terminal carbon with one to three substituents independently selected from R₁₄;

R₁₅ is selected from the group consisting of hydroxy, amino, NO₂ and R₆;

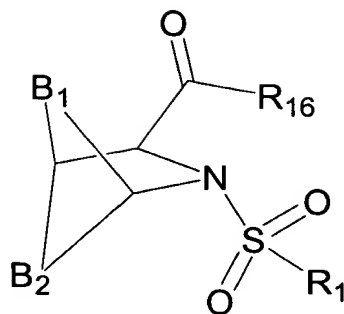
R₆ is optionally present and is one to three substituents independently selected from the group consisting of halogen, C₁₋₈alkoxy, R₁₀, R₁₂, -N(R₁₁)C(O)-R₁₀, -N(R₁₁)C(O)-R₁₂, -N(R₁₁)SO₂-R₁₀, -N(R₁₁)SO₂-R₁₂, -N(R₁₁)C(O)-N(R₁₁,R₁₀), -N(R₁₁)C(O)-N(R₁₁,R₁₂), -N(R₁₁)C(O)-N(R₁₂,R₁₇), -C(O)-N(R₁₁,R₁₀), -C(O)-N(R₁₁,R₁₂), -C(O)-N(R₁₂,R₁₇), -OC(O)-N(R₁₁,R₁₀), -OC(O)-N(R₁₁,R₁₂), -OC(O)-N(R₁₂,R₁₇), -OC(O)-R₁₀, -OC(O)-R₁₂, -O-R₁₀ and R₁₀-(C₁₋₈)alkoxy;

R₁₁ is selected from the group consisting of hydrogen and C₁₋₈alkyl; and,

B₁ and B₂ are independently selected from the group consisting of C₁₋₈alkylene and C₂₋₈alkenylene optionally substituted with one to two substituents independently selected from the group consisting of halogen, hydroxy, hydroxy(C₁₋₈)alkyl, hydroxy(C₁₋₈)alkoxy, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₁₋₈alkoxy, carboxyl, amino, *N*-(C₁₋₈alkyl)amino, *N,N*-(C₁₋₈dialkyl)amino, -CF₃ and -OCF₃;

and pharmaceutically acceptable salts, racemic mixtures, diastereomers and enantiomers thereof;

comprising reacting a compound of Formula (IV)

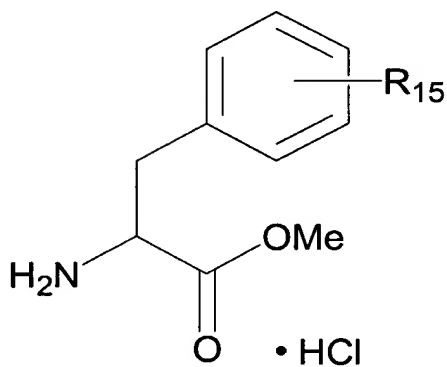


Formula (IV)

wherein

R₁₆ is selected from the group consisting of halogen, mixed anhydride and hydroxy;

with a compound of Formula (V)



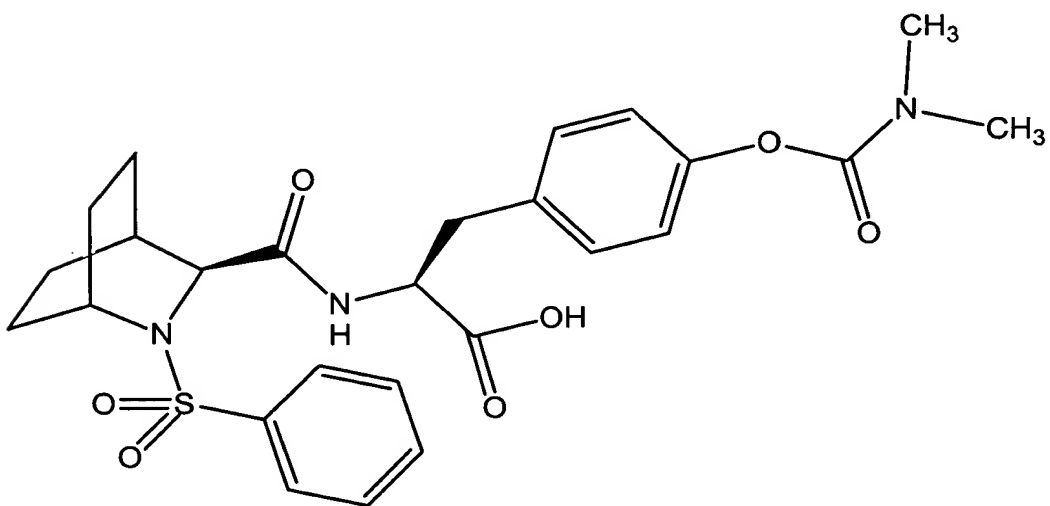
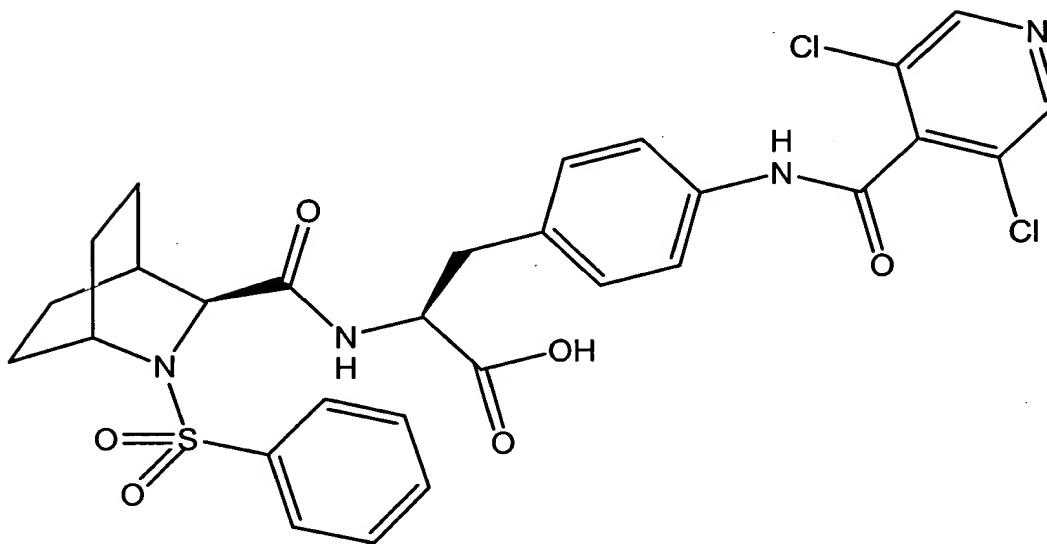
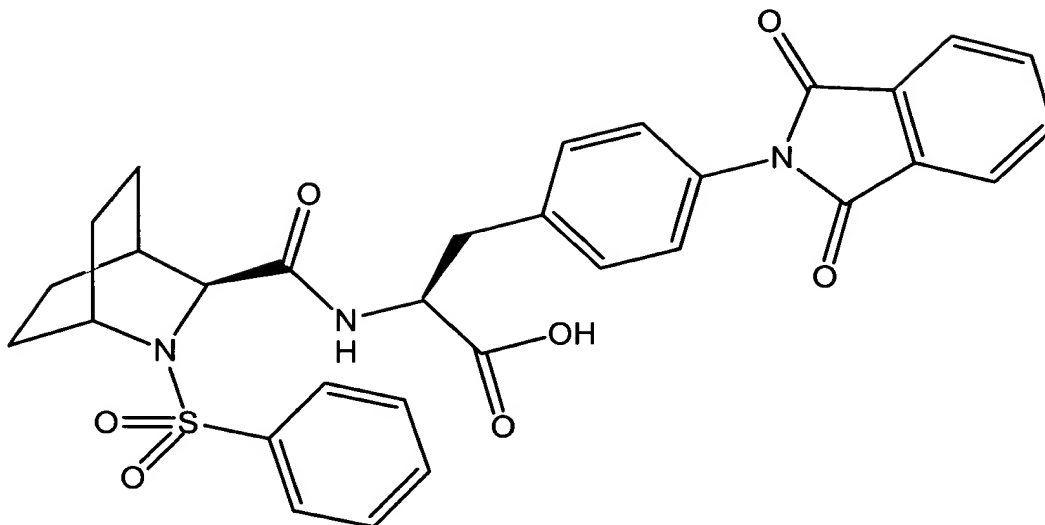
Formula (V);

in the presence of appropriate coupling agents, bases and solvents to form the compound of Formula (II).

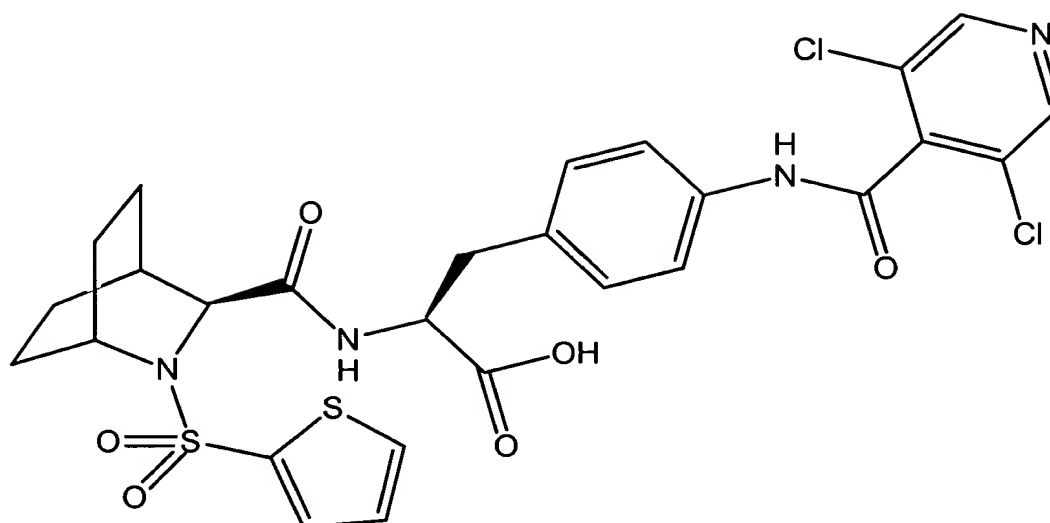
In a preferred embodiment of the process of the present invention, R₁₅ is a substituent selected from the group consisting of hydroxy, iodine, bromine and NO₂.

Other preferred embodiments include compounds of Formula (I) selected from compounds of the formula:

09821602-09821601



and,



The compounds of the present invention may also be present in the form of pharmaceutically acceptable salts. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts" (*Ref. International J. Pharm.*, **1986**, 33, 201-217; *J. Pharm.Sci.*, **1997** (Jan), 66, 1, 1). Other salts may, however, be useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts. Representative organic or inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydriodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic acid. Representative organic or inorganic bases include, but are not limited to, basic or cationic salts such as benzathine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium and zinc.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present

invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the subject. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. Where the processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form or as individual enantiomers or diastereomers by either stereospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers or diastereomers by standard techniques, such as the formation of stereoisomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of stereoisomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column. It is to be understood that all stereoisomers, racemic mixtures, diastereomers and enantiomers thereof are encompassed within the scope of the present invention.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press,

1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known in the art.

5 Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention.

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As used herein, unless otherwise noted, "alkyl" and "alkoxy" whether used alone or as part of a substituent group refers to straight and branched carbon chains having 1 to 8 carbon atoms or any number within this range. Similarly, alkenyl and alkynyl groups include straight and branched chain alkenes and alkynes having 2 to 8 carbon atoms or any number within this range, wherein an alkenyl chain has at least one double bond in the chain and an alkynyl chain has at least one triple bond in the chain. Alkoxy radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups.

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As used herein, unless otherwise noted "oxo" whether used alone or as part of a substituent group refers to an O= to either a carbon or a sulfur atom. For example, phthalimide and saccharin are examples of compounds with oxo substituents.

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The term "cycloalkyl," as used herein, refers to an optionally substituted, stable, saturated or partially saturated monocyclic or bicyclic ring system containing from 3 to 8 ring carbons and preferably 5 to 7 ring carbons. Examples of such cyclic alkyl rings include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

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The term "heterocyclyl" as used herein refers to an optionally substituted, stable, saturated or partially saturated 5 or 6 membered monocyclic or bicyclic

ring systems which consists of carbon atoms and from one to three heteroatoms selected from N, O or S. Examples of heterocyclyl groups include, but are not limited to, pyrrolinyl (including 2*H*-pyrrole, 2-pyrrolinyl or 3-pyrrolinyl), pyrrolidinyl, dioxolanyl, 2-imidazoliny, imidazolidinyl, 2-pyrazoliny, pyrazolidinyl, piperidinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl or piperazinyl. The heterocyclyl group may be attached at any heteroatom or carbon atom which results in the creation of a stable structure.

The term "aryl", as used herein, refers to optionally substituted aromatic groups comprising a stable six membered monocyclic or ten membered bicyclic aromatic ring system which consists of carbon atoms. Examples of aryl groups include, but are not limited to, phenyl or naphthalenyl.

The term "heteroaryl" as used herein represents a stable five or six membered monocyclic aromatic ring system or a nine or ten membered benzo-fused heteroaromatic ring system which consists of carbon atoms and from one to three heteroatoms selected from N, O or S. The heteroaryl group may be attached at any heteroatom or carbon atom which results in the creation of a stable structure.

The term "arylalkyl" means an alkyl group substituted with an aryl group (e.g., benzyl, phenethyl). The term "arylalkoxy" indicates an alkoxy group substituted with an aryl group (e.g., benzyloxy, phenethoxy, etc.). Similarly, the term "aryloxy" indicates an oxy group substituted with an aryl group (e.g., phenoxy).

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aralkyl, alkylamino) it shall be interpreted as including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C₁₋₆) shall refer independently to the number of carbon atoms in an alkyl or cycloalkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

The aza-bridged-bicyclic amino acid compounds of the present invention are useful $\alpha 4$ integrin receptor antagonists and, more particularly, $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin receptor antagonists for treating a variety of integrin mediated disorders that are ameliorated by inhibition of the $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin receptor including, but not limited to, inflammatory, autoimmune and cell-proliferative disorders.

Illustrative of the invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and any of the compounds described above. Also illustrative of the invention is a pharmaceutical composition made by mixing any of the compounds described above and a pharmaceutically acceptable carrier. A further illustration of the invention is a process for making a pharmaceutical composition comprising mixing any of the compounds described above and a pharmaceutically acceptable carrier. The present invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier.

An example of the invention is a method for the treatment of integrin mediated disorders in a subject in need thereof comprising administering to the subject a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. Also included in the invention is the use of a compound of Formula (I) for the preparation of a medicament for treating an integrin mediated disorder in a subject in need thereof.

Further exemplifying the invention is the method for the treatment of

integrin mediated disorders, wherein the therapeutically effective amount of the compound is from about 0.01 mg/kg/day to about 30 mg/kg/day.

5 In accordance with the methods of the present invention, the individual components of the pharmaceutical compositions described herein can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted
10 accordingly.

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

15 The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human, that is being sought by a researcher, veterinarian, medical doctor, or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.
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As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the
25 specified ingredients in the specified amounts.

30 The utility of the compounds to treat integrin mediated disorders can be determined according to the procedures herein. The present invention therefore provides a method for the treatment of integrin mediated disorders in a subject in need thereof which comprises administering any of the compounds as defined herein in a quantity effective to inhibit the $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin receptor including, but not limited to, inflammatory, autoimmune and cell-proliferative disorders. Accordingly, a compound of the present invention

may be administered by any conventional route of administration including, but not limited to oral, nasal, pulmonary, sublingual, ocular, transdermal, rectal, vaginal and parenteral (i.e. subcutaneous, intramuscular, intradermal, intravenous etc.).

5

To prepare the pharmaceutical compositions of this invention, one or more compounds of Formula (I) or salt thereof as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration (e.g. oral or parenteral). Suitable pharmaceutically acceptable carriers are well known in the art. Descriptions of some of these pharmaceutically acceptable carriers may be found in The Handbook of Pharmaceutical Excipients, published by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain.

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Methods of formulating pharmaceutical compositions have been described in numerous publications such as Pharmaceutical Dosage Forms: Tablets, Second Edition, Revised and Expanded, Volumes 1-3, edited by Lieberman et al; Pharmaceutical Dosage Forms: Parenteral Medications, Volumes 1-2, edited by Avis et al; and Pharmaceutical Dosage Forms: Disperse Systems, Volumes 1-2, edited by Lieberman et al; published by Marcel Dekker, Inc.

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In preparing a pharmaceutical composition of the present invention in liquid dosage form for oral, topical and parenteral administration, any of the usual pharmaceutical media or excipients may be employed. Thus, for liquid dosage forms, such as suspensions (i.e. colloids, emulsions and dispersions) and solutions, suitable carriers and additives include but are not limited to pharmaceutically acceptable wetting agents, dispersants, flocculation agents, thickeners, pH control agents (i.e. buffers), osmotic agents, coloring agents, flavors, fragrances, preservatives (i.e. to control microbial growth, etc.) and a liquid vehicle may be employed. Not all of the components listed above will be

required for each liquid dosage form.

In solid oral preparations such as, for example, dry powders for reconstitution or inhalation, granules, capsules, caplets, gelcaps, pills and tablets (each including immediate release, timed release and sustained release formulations), suitable carriers and additives include but are not limited to diluents, granulating agents, lubricants, binders, glidants, disintegrating agents and the like. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated, gelatin coated, film coated or enteric coated by standard techniques.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient necessary to deliver an effective dose as described above. The pharmaceutical compositions herein will contain, per unit dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, of from about 0.01 mg/kg to about 300 mg/kg (preferably from about 0.01 mg/kg to about 100 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) and may be given at a dosage of from about 0.01 mg/kg/day to about 300 mg/kg/day (preferably from about 0.01 mg/kg/day to about 100 mg/kg/day and more preferably from about 0.01 mg/kg/day to about 30 mg/kg/day). Preferably, the method for the treatment of integrin mediated disorders described in the present invention using any of the compounds as defined herein, the dosage form will contain a pharmaceutically acceptable carrier containing between from about 0.01 mg to about 100 mg; and, more preferably, from about 5 mg to about 50 mg of the compound, and may be constituted into any form suitable for the mode of administration selected. The dosages, however, may be varied depending upon the requirement of the subjects, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

5 Preferably these compositions are in unit dosage forms from such as
tablets, pills, capsules, dry powders for reconstitution or inhalation, granules,
lozenges, sterile parenteral solutions or suspensions, metered aerosol or liquid
10 sprays, drops, ampoules, autoinjector devices or suppositories for
administration by oral, intranasal, sublingual, intraocular, transdermal,
parenteral, rectal, vaginal, dry powder inhaler or other inhalation or insufflation
means. Alternatively, the composition may be presented in a form suitable for
once-weekly or once-monthly administration; for example, an insoluble salt of
15 the active compound, such as the decanoate salt, may be adapted to provide a
depot preparation for intramuscular injection.

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15 For preparing solid pharmaceutical compositions such as tablets, the
principal active ingredient is mixed with a pharmaceutical carrier, e.g.
conventional tableting ingredients such as diluents, binders, adhesives,
disintegrants, lubricants, antiadherents and glidants. Suitable diluents include,
but are not limited to, starch (i.e. corn, wheat, or potato starch, which may be
20 hydrolized), lactose (granulated, spray dried or anhydrous), sucrose, sucrose-
based diluents (confectioner's sugar; sucrose plus about 7 to 10 weight
percent invert sugar; sucrose plus about 3 weight percent modified dextrans;
sucrose plus invert sugar, about 4 weight percent invert sugar, about 0.1 to 0.2
weight percent cornstarch and magnesium stearate), dextrose, inositol,
25 mannitol, sorbitol, microcrystalline cellulose (i.e. AVICEL TM microcrystalline
cellulose available from FMC Corp.), dicalcium phosphate, calcium sulfate
dihydrate, calcium lactate trihydrate and the like. Suitable binders and
adhesives include, but are not limited to acacia gum, guar gum, tragacanth
gum, sucrose, gelatin, glucose, starch, and cellulose (i.e. methylcellulose,
sodium carboxymethylcellulose, ethylcellulose, hydroxypropylmethylcellulose,
hydroxypropylcellulose, and the like), water soluble or dispersible binders (i.e.
30 alginic acid and salts thereof, magnesium aluminum silicate,
hydroxyethylcellulose [i.e. TYLOSE TM available from Hoechst Celanese],
polyethylene glycol, polysaccharide acids, bentonites, polyvinylpyrrolidone,
polymethacrylates and pregelatinized starch) and the like. Suitable

disintegrants include, but are not limited to, starches (corn, potato, etc.), sodium starch glycolates, pregelatinized starches, clays (magnesium aluminum silicate), celluloses (such as crosslinked sodium carboxymethylcellulose and microcrystalline cellulose), alginates, pregelatinized starches (i.e. corn starch, etc.), gums (i.e. agar, guar, locust bean, karaya, pectin, and tragacanth gum), cross-linked polyvinylpyrrolidone and the like. Suitable lubricants and antiadherents include, but are not limited to, stearates (magnesium, calcium and sodium), stearic acid, talc waxes, stearrowet, boric acid, sodium chloride, DL-leucine, carbowax 4000, carbowax 6000, sodium oleate, sodium benzoate, sodium acetate, sodium lauryl sulfate, magnesium lauryl sulfate and the like. Suitable gildants include, but are not limited to, talc, cornstarch, silica (i.e. CAB-O-SIL™ silica available from Cabot, SYLOID™ silica available from W.R. Grace/Davison, and AEROSIL™ silica available from Degussa) and the like. Sweeteners and flavorants may be added to chewable solid dosage forms to improve the palatability of the oral dosage form. Additionally, colorants and coatings may be added or applied to the solid dosage form for ease of identification of the drug or for aesthetic purposes. These carriers are formulated with the pharmaceutical active to provide an accurate, appropriate dose of the pharmaceutical active with a therapeutic release profile.

Generally these carriers are mixed with the pharmaceutical active to form a solid preformulation composition containing a homogeneous mixture of the pharmaceutical active of the present invention, or a pharmaceutically acceptable salt thereof. Generally the preformulation will be formed by one of three common methods: (a) wet granulation, (b) dry granulation and (c) dry blending. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from about 0.1 mg to about 500 mg of the active ingredient of the present invention. The tablets or pills containing the novel compositions may also be formulated in multilayer tablets or pills to

provide a sustained or provide dual-release products. For example, a dual release tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer, which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric materials such as shellac, cellulose acetate (i.e. cellulose acetate phthalate, cellulose acetate trimetllitate), polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, methacrylate and ethylacrylate copolymers, methacrylate and methyl methacrylate copolymers and the like. Sustained release tablets may also be made by film coating or wet granulation using slightly soluble or insoluble substances in solution (which for a wet granulation acts as the binding agents) or low melting solids a molten form (which in a wet granulation may incorporate the active ingredient). These materials include natural and synthetic polymers waxes, hydrogenated oils, fatty acids and alcohols (i.e. beeswax, carnauba wax, cetyl alcohol, cetylstearyl alcohol, and the like), esters of fatty acids metallic soaps, and other acceptable materials that can be used to granulate, coat, entrap or otherwise limit the solubility of an active ingredient to achieve a prolonged or sustained release product.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include, but are not limited to aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable suspending agents for aqueous suspensions, include synthetic and natural gums such as, acacia, agar, alginate (i.e. propylene alginate, sodium alginate and the like), guar, karaya, locust bean, pectin, tragacanth, and xanthan gum, cellulose such as sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose and hydroxypropyl

methycellulose, and combinations thereof, synthetic polymers such as polyvinyl pyrrolidone, carbomer (i.e. carboxypolymethylene), and polyethylene glycol; clays such as bentonite, hectorite, attapulgate or sepiolite; and other pharmaceutically acceptable suspending agents such as lecithin, gelatin or the like. Suitable surfactants include but are not limited to sodium docusate, sodium lauryl sulfate, polysorbate, octoxynol-9, nonoxynol-10, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polyoxamer 188, polyoxamer 235 and combinations thereof. Suitable deflocculating or dispersing agent include pharmaceutical grade lecithins. Suitable flocculating agent include but are not limited to simple neutral electrolytes (i.e. sodium chloride, potassium, chloride, and the like), highly charged insoluble polymers and polyelectrolyte species, water soluble divalent or trivalent ions (i.e. calcium salts, alums or sulfates, citrates and phosphates (which can be used jointly in formulations as pH buffers and flocculating agents). Suitable preservatives include but are not limited to parabens (i.e. methyl, ethyl, *n*-propyl and *n*-butyl), sorbic acid, thimerosal, quaternary ammonium salts, benzyl alcohol, benzoic acid, chlorhexidine gluconate, phenylethanol and the like. There are many liquid vehicles that may be used in liquid pharmaceutical dosage forms, however, the liquid vehicle that is used in a particular dosage form must be compatible with the suspending agent(s). For example, nonpolar liquid vehicles such as fatty esters and oils liquid vehicles are best used with suspending agents such as low HLB (Hydrophile-Lipophile Balance) surfactants, stearylalcohol hectorite, water insoluble resins, water insoluble film forming polymers and the like. Conversely, polar liquids such as water, alcohols, polyols and glycols are best used with suspending agents such as higher HLB surfactants, clays silicates, gums, water soluble cellulose, water soluble polymers and the like. For parenteral administration, sterile suspensions and solutions are desired. Liquid forms useful for parenteral administration include sterile solutions, emulsions and suspensions. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

Furthermore, compounds of the present invention can be administered in an intranasal dosage form via topical use of suitable intranasal vehicles or via

transdermal skin patches, the composition of which are well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the administration of a therapeutic dose will, of course, be continuous rather than intermittent throughout the dosage regimen.

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Compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, multilamellar vesicles and the like. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, phosphatidylcholines and the like.

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Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include, but are not limited to polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxy-ethylaspartamidephenol, or polyethyl eneoxydepolylysine substituted with palmitoyl residue. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, to homopolymers and copolymers (which means polymers containing two or more chemically distinguishable repeating units) of lactide (which includes lactic acid d-, l- and meso lactide), glycolide (including glycolic acid), ϵ -caprolactone, p-dioxanone (1,4-dioxan-2-one), trimethylene carbonate (1,3-dioxan-2-one), alkyl derivatives of trimethylene carbonate, δ -valerolactone, β -butyrolactone, γ -butyrolactone, ϵ -decalactone, hydroxybutyrate, hydroxyvalerate, 1,4-dioxepan-2-one (including its dimer 1,5,8,12-tetraoxacyclotetradecane-7,14-dione), 1,5-dioxepan-2-one, 6,6-dimethyl-1,4-dioxan-2-one, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels and blends thereof.

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Compounds of this invention may be administered in any of the foregoing

compositions and dosage regimens or by means of those compositions and dosage regimens established in the art whenever treatment of integrin mediated disorders is required for a subject in need thereof.

5 The daily dose of a pharmaceutical composition of the present invention may be varied over a wide range from about 0.7 mg to about 21,000 mg per adult human per day; preferably, the dose will be in the range of from about 0.7 mg to about 7000 mg per adult human per day; most preferably the dose will be in the range of from about 0.7 mg to about 2100 mg per adult human per day.
10 For oral administration, the compositions are preferably provided in the form of tablets containing, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.01 mg/kg to about 300 mg/kg of body weight per day. Preferably, the range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day; and, most preferably, from about 0.01 mg/kg to about 30 mg/kg of body weight per day. Advantageously, a compound of the present invention may be administered in a single daily dose or the total daily dosage may be administered in divided doses of two, three or four times daily.

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25 Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation, and the advancement of the disease condition. In addition, factors associated with the particular subject being treated, including subject age, weight, diet and time of administration, will result in the need to adjust the dose to an appropriate therapeutic level.

30 Abbreviations used in the instant specification, particularly the Schemes and Examples, are as follows:

| | |
|-----|-----------------------------|
| BSA | Bovine Serum Albumen |
| DBC | 2,6-Dichlorobenzoylchloride |

| | | |
|----|-------------------|---|
| | DCM | Dichloromethane |
| | DIEA | Diisopropylethylamine |
| | DMF | N, N-Dimethylformamide |
| | EDAC | N-ethyl-N'-dimethylaminopropylcarbodiimide hydrochloride |
| 5 | Et ₂ O | Diethyl ether |
| | EtOAc | Ethyl acetate |
| | EtOH | Ethanol |
| | h | hour |
| 10 | HATU | O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate |
| | HPLC | High Performance Liquid Chromatography |
| | Me | Methyl |
| | MeOH | Methanol |
| | min | Minutes |
| 15 | PBS | Phosphate Buffer Solution |
| | Ph | Phenyl |
| | rt | Room temperature |
| | SDS | Sodium Dodecasulfate |
| | THF | Tetrahydrofuran |
| 20 | Thi | Thienyl |
| | TMS | Tetramethylsilane |
| | TFA | Trifluoroacetic acid |
| | Tol | Toluene |

General Synthetic Methods

Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below and are illustrated more particularly in the scheme that follows. Since the scheme is an illustration, the invention should not be construed as being limited by the chemical reactions and conditions expressed. The preparation of the various starting materials used in the schemes is well within the skill of persons versed in the art.

Scheme AA describes a general synthetic method whereby intermediate and target compounds of the present invention may be prepared. Additional representative compounds and stereoisomers, racemic mixtures, diastereomers and enantiomers thereof can be synthesized using the intermediates prepared in accordance with the Schemes AA and other

materials, compounds and reagents known to those skilled in the art. All such compounds, stereoisomers, racemic mixtures, diastereomers and enantiomers thereof are intended to be encompassed within the scope of the present invention. Since the scheme is an illustration, the invention should not be construed as being limited by the chemical reactions and conditions expressed. The preparation of the various starting materials used in the scheme is well within the skill of persons versed in the art.

In the following general method for preparing compounds of the invention, isocyanate Compound **AA1** was condensed with ethyl glyoxalate to form a derivative of Compound **AA1** which underwent [4+2] cycloaddition with cyclohexadiene to furnish Compound **AA2**, having a [2.2.2] bicyclic ring system. Other compounds of the present invention having a tosyl substituent were prepared using appropriate reagents and starting materials known to those skilled in the art, such as using tosyl isocyanate for Compound **AA1**. Similarly, additional compounds of the present invention having [2.2.1] or [2.1.1] bicyclic ring systems were prepared using appropriate reagents and starting materials known to those skilled in the art for the cycloaddition of the derivative of Compound **AA1**.

Compound **AA2** was reduced by hydrogenation and saponified with sodium hydroxide to yield the acid Compound **AA3**. Other compounds of the present invention having a double bond in the bicyclic ring system may be prepared by avoiding the reduction step. Optionally, a hydroxy substituent is attached to the bicyclic ring system of Compound **AA2** by hydroboration; further substitutions on the bicyclic ring system, by replacement of the hydroxy group, may be carried out by methods known to those skilled in the art.

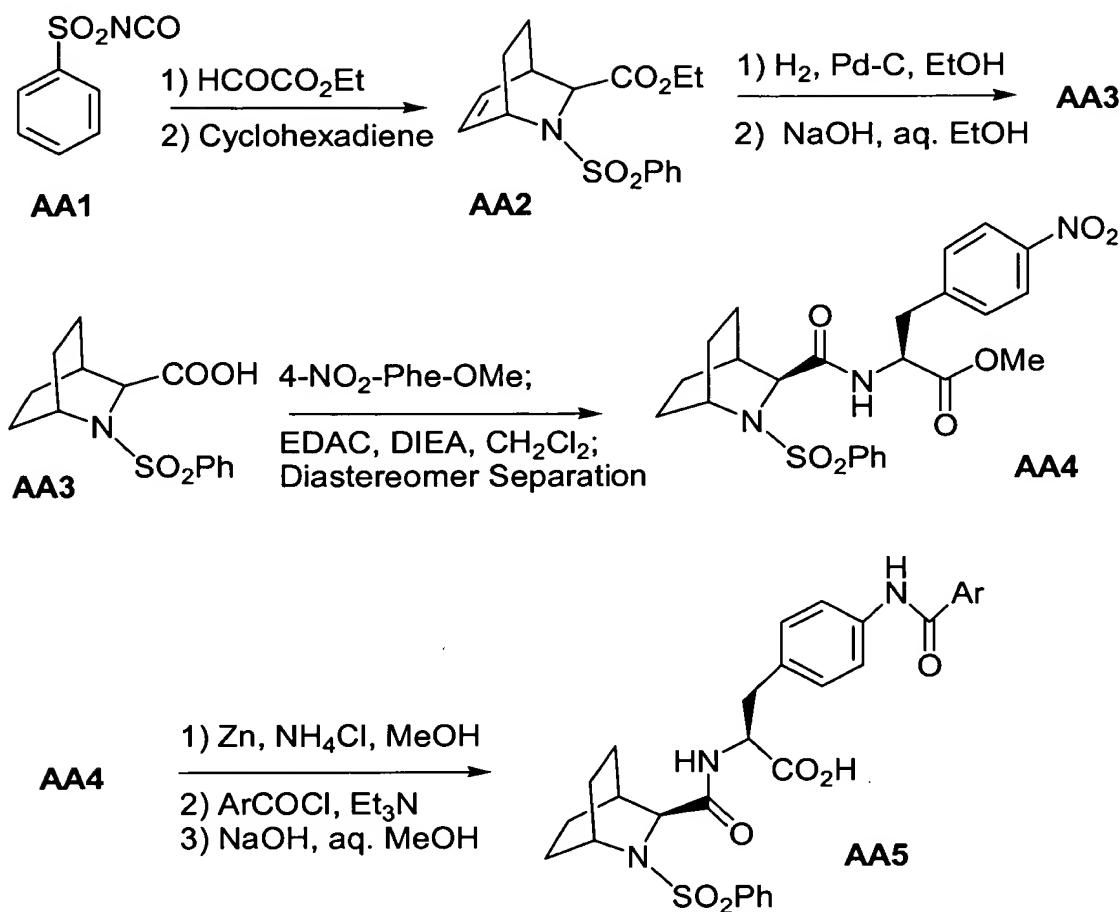
(S)-4-Nitrophenylalanine methyl ester was acylated with Compound **AA3**, in the presence an appropriate coupling agent, base and solvent. An appropriate coupling agent may include, and is not limited to, EDAC hydrochloride, DIC, DCC or HATU; an appropriate base may include, and is not limited to, DIEA; and, an appropriate solvent may include, and is not limited

to, CH₂Cl₂ (DCM) or DMF. For compounds of the present invention, (S)-4-Nitrophenylalanine methyl ester was acylated with Compound **AA3** in the presence of EDAC, DIEA and DCM. Other compounds of the present invention may obviously be prepared by acylating (S)-4-Nitrophenylalanine methyl ester with Compound **AA3** in the presence of appropriate coupling agents, bases and solvents.

The (S,S) diastereomer Compound **AA4** was separated, the nitro group was reduced with zinc dust and the resultant amine intermediate was acylated with 2,6-dichlorobenzoyl chloride and the ester saponified with sodium hydroxide to afford Compound **AA5**. Other compounds of the present invention having a variety of substituents attached to the amide linker of Compound **AA5** were prepared by acylating the amine intermediate resulting from the reduction of Compound **AA4** with appropriate starting materials known to those skilled in the art.

Similarly, additional compounds of the present invention having a variety of substituents attached directly to the benzyl group of Compound **AA4** were prepared by acylating Compound **AA3** with appropriate starting materials known to those skilled in the art.

SCHEME AA



Specific Synthetic Methods

Specific compounds which are representative of this invention were prepared as per the following examples and reaction sequences; the examples and the diagrams depicting the reaction sequences are offered by way of illustration, to aid in the understanding of the invention and should not be construed to limit in any way the invention set forth in the claims which follow thereafter. The instant compounds may also be used as intermediates in subsequent examples to produce additional compounds of the present invention. No attempt has been made to optimize the yields obtained in any of the reactions. One skilled in the art would know how to increase such yields through routine variations in reaction times, temperatures, solvents and/or reagents.

Reagents were purchased from commercial sources. Microanalyses were performed at Robertson Microlit Laboratories, Inc., Madison, New Jersey and are expressed in percentage by weight of each element per total molecular weight.

Nuclear magnetic resonance (NMR) spectra for hydrogen atoms were measured in the indicated solvent with (TMS) as the internal standard on a Bruker AM-360 (360 MHz) spectrometer. The values are expressed in parts per million down field from TMS. The mass spectra (MS) were determined on a Micromass Platform LC spectrometer using electrospray techniques as either (ESI) m/z (M+H⁺) or (ESI) m/z (M-H⁺). Stereoisomeric compounds may be characterized as racemic mixtures or as separate diastereomers and enantiomers thereof using X-ray crystallography and other methods known to one skilled in the art. Unless otherwise noted, the materials used in the examples were obtained from readily available commercial suppliers or synthesized by standard methods known to one skilled in the art of chemical synthesis. The substituent groups, which vary between examples, are hydrogen unless otherwise noted.

Example 1

4-[(2,6-dichlorobenzoyl)amino]-*N*-[[[(3*S*)-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-*L*-phenylalanine (Compound **6a**)

A mixture of benzenesulfonyl isocyanate Compound **BB1** (18.3 g, 0.10 mol), 20 mL of ethyl glyoxalate (50% solution in toluene, 0.10 mol) and 50 mL of dry toluene was heated at reflux under nitrogen atmosphere for 24 h, then 1,3-cyclohexadiene (20 mL, 0.21 mol) was added in one portion. The mixture was heated for 10 h then cooled to rt, and the white precipitate was filtered off and recrystallized from EtOAc to afford a white crystalline material Compound **BB2** (19.1 g).

A suspension of Compound **BB2** (19.0 g) with 10% Pd/C (200 mg) and 200 mL of EtOH was hydrogenated for 24 h. The mixture was filtered through celite, and the filtrate was concentrated in vacuo. The residue was recrystallized from EtOAc providing 16.1 g of Compound **BB3** (white crystals, ¹H NMR (CDCl₃) 7.98 (d, J=7, 2H), 7.5 (m, 3H), 4.36 (m, 1H), 4.25 (q, J=8, 2H), 3.65 (d, J=3, 1H), 2.22 (m, 1H), 2.0 (m, 1H), 1.9 (m, 1H), 1.5 (broad m, 6H), 1.28 (t, J=8, 3H). A solution of Compound **BB3** in 200 mL of EtOH and 50 mL of 3N NaOH (aq) was stirred for 24 h. The EtOH was removed in vacuo, and the residue was dissolved in 300 mL of water, washed with EtOAc and the organic layer

was discarded. The aqueous layer was acidified to pH 2 with 1N HCl (aq), then extracted repeatedly with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated to yield 9.5 g of white crystalline Compound **BB4**. ¹H NMR (CDCl₃) 7.98 (d, J=7, 2H), 7.5 (m, 3H), 4.36 (m, 1H), 3.70 (d, J=3, 1H), 2.30 (m, 1H), 2.0 (m, 1H), 1.9-1.3 (broad m, 7H).

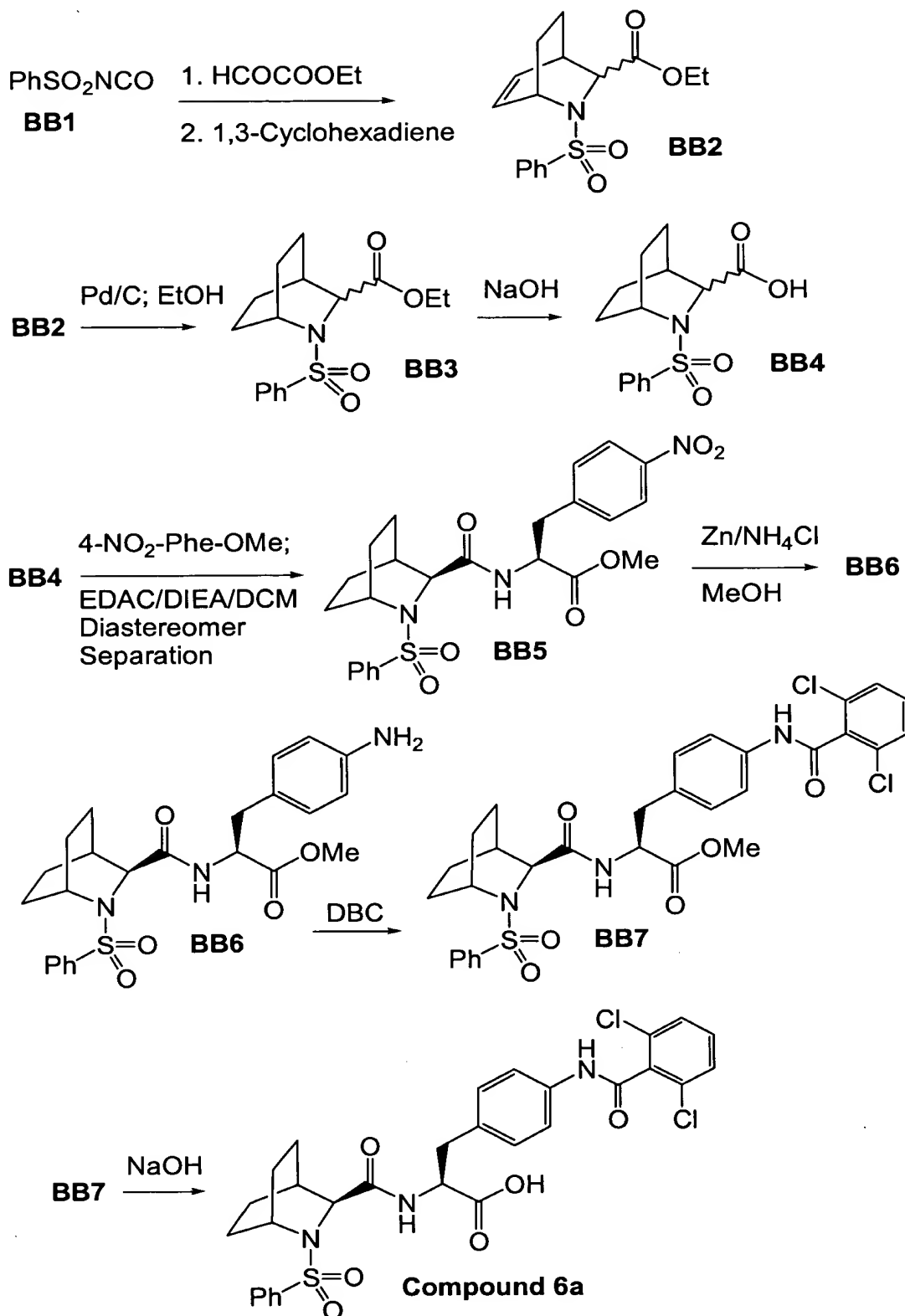
A mixture of Compound **BB4**, (S)-4-nitrophenylalanine methyl ester hydrochloride (6.75 g, 1 eq), EDAC hydrochloride (5.0 g), DIEA (3 eq) and 150 mL DCM was stirred for 5 h at room temperature, washed sequentially with 50 mL of NaHCO₃ (sat'd aq) and 1 N HCl (50 mL), dried (sodium sulfate), and concentrated to give a white solid foam (12.0 g). The solid material was crystallized from hexane-ethyl acetate to afford colorless crystals of Compound **BB5** as the (S,S) diastereomer (1.05 g), NMR (CDCl₃) 8.14 (d, J=8, 2H), 7.90 (d, J=7, 2H), 7.62 (t, J=7, 1H), 7.52 (t, J=7, 2H), 7.38 (d, J=8, 2H), 2.3 (m, 1H), 4.95 (q, J=8, 1H). The stereochemistry of Compound **BB5** was confirmed by X-ray analysis. The mother liquor was concentrated and the residue was purified by column chromatography (silica gel; hexane:ethyl acetate, 1:1) to afford a second amide (R,S) diastereomer.

A solution of 1.00 g of Compound **BB5** in MeOH was treated with NH₄Cl (0.54 g, 5 eq) and zinc dust (4.5 g, 35 eq) and stirred under reflux for 3 h. The reaction was filtered through celite and the filtrate was evaporated. The residue was treated with 10% acetic acid (1 mL), neutralized with sodium bicarbonate, and the product was extracted with EtOAc (3 X 50 mL). The organic layer was washed with water (15 mL), dried (Na₂SO₄), and concentrated to give Compound **BB6** as a white solid (0.85 g, MS m/e 472.6 (MH⁺)). A solution of Compound **BB6**, DCM (9 mL), and TEA (0.24 g, 0.0024 mol) at rt was treated with DBC (0.453 g, 1.2 eq) and stirred for 6 h. The reaction was diluted with DCM (50 mL), washed with saturated sodium bicarbonate (20 mL), dried (Na₂SO₄), and concentrated. The residue was purified by column chromatography (silica gel; 1:1 ethylacetate:hexane) to afford Compound **BB7** as a white solid (1.05 g).

A solution Compound **BB7** in 30 mL of MeOH and 10 mL of 3N NaOH (aq) was stirred for 24 h. MeOH was removed in vacuo, and the residue was dissolved in 100 mL of water, washed with EtOAc. The aqueous layer was acidified to pH 2 with 1N HCl (aq) and extracted with EtOAc (3 X). The combined organic layers were dried over MgSO₄, and concentrated to provide 0.76 g of white crystalline Compound **6a**. (ESI) *m/z* 628 (free acid, M-H⁻). ¹H NMR (CDCl₃) 7.98 (s, 1H), 7.89 (d, J=8, 2H), 7.65 (m, 2H), 7.54 (t, J=8, 2H), 7.25 (m, 6H), 7.12 (d, J=7, 1H), 4.93 (q, J=7, 1H), 4.08 (d, J=3, 1H), 3.83 (m, 1 H), 3.33 (dd, J=13 and 6, 1H), 3.16 (dd, J=13 and 7, 1H), 2.22 (m, 1H), 1.8-1.0 (m, 8H).

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Using the procedure of Example 1 and the appropriate reagents and starting materials known to those skilled in the art, other compounds of the present

invention may be prepared including, but not limited to:

| Cpd | | (M-H) | (M+H ⁺) |
|-----|--|-------|---------------------|
| 1 | 4-[(2,6-dichlorobenzoyl)amino]-N-[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 642 | --- |
| 2 | 4-[(2,4,6-trichlorobenzoyl) amino]-N-[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 676 | --- |
| 3 | 4-[(2,6-dimethoxybenzoyl)amino]-N-[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 634 | --- |
| 6 | 4-[(2,6-dichlorobenzoyl)amino]-N-[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 628 | --- |
| 6b | 4-[(2,6-dichlorobenzoyl)amino]-N-[[2-[(3R)-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 628 | 630 |
| 9 | 4-[(2-methylbenzoyl)amino]-N-[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-(α^1 S)-phenylalanine; | 588 | --- |
| 10 | 4-[(2-chlorobenzoyl)amino]-N-[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 608 | --- |
| 11 | 4-[(2,6-difluorobenzoyl)amino]-N-[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 610 | --- |
| 12 | 4-[[2-(trifluoromethyl)benzoyl]amino]-N-[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 642 | --- |
| 13 | 4-[[2-(trifluoromethoxy)benzoyl]amino]-N-[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 658 | --- |
| 14 | 4-[(2-bromobenzoyl)amino]-N-[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 666 | 655 |
| 15 | 4-[(2,6-difluorobenzoyl)amino]-N-[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 596 | --- |
| 25 | 4-(benzoylamino)-N-[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 575 | --- |
| 26 | 4-[[4-(2,5-dimethoxybenzoyl)benzoyl]amino]-N- | --- | 740 |

| | | | |
|----|--|-----|-----|
| | [[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | | |
| 27 | 4-[[[(2,6-dichlorophenyl)acetyl]amino]-N-[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 658 | --- |
| 28 | 4-[[[(2,6-dichlorophenyl)amino]carbonyl]amino]-N-[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 643 | --- |
| 29 | 4-[(2,6-dichlorophenyl)methoxy]-N-[[[(3S)-2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 617 |
| 30 | 4-(phenylmethoxy)-N-[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 561 | --- |
| 31 | 4-[[[2,4,6-tris(1-methylethyl)benzoyl]amino]-N-[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 701 | 702 |
| 34 | 4-[[[(2,6-difluorophenyl)amino]carbonyl]amino]-N-[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 611 | 612 |
| 35 | 3-[(2,6-difluorobenzoyl)amino]-N-[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 610 | --- |
| 36 | 3-[(2,6-dimethoxybenzoyl)amino]-N-[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]phenylalanine; | 635 | 636 |
| 37 | 3-[(2,6-dichlorobenzoyl)amino]-N-[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]phenylalanine; | 644 | 645 |
| 38 | O-[(2,6-dichlorophenyl)methyl]-methyl-N-[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]tyrosine; | --- | 631 |
| 39 | 4-[(2,6-dichlorobenzoyl)amino]-N-methyl-N-[[[(3R)-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 644 |
| 40 | O-[(2,6-dichlorophenyl)methyl]-N-[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-5-en-3-yl]carbonyl]-L-tyrosine; | --- | 616 |
| 41 | O-[(2,6-dichlorophenyl)methyl]-N-[[[(3R)-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-tyrosine; | --- | 617 |
| 42 | 4-[(2,6-dichlorobenzoyl)amino]-N-[[2- | --- | 628 |

| | | | |
|-----|---|-----|-----|
| | (phenylsulfonyl)-2-azabicyclo[2.2.2]oct-5-en-3-yl]carbonyl]-L-phenylalanine; | | |
| 43 | 4-[(2,4,6-trifluorobenzoyl)amino]- <i>N</i> -[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 614 | --- |
| 44 | 4-[(2,3,5,6-tetrafluorobenzoyl)amino]- <i>N</i> -[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 634 |
| 48 | 4-[(2-carboxybenzoyl)amino]- <i>N</i> -[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 606 |
| 50 | 4-[(4-pyridinylcarbonyl)amino]- <i>N</i> -[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 563 |
| 50a | 4-[(4-pyridinylcarbonyl)amino]- <i>N</i> -[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 563 |
| 51 | 4-[[2-(2,6-dichlorophenyl)sulfonyl]amino]- <i>N</i> -[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 666 |
| 53 | 4-[[1-[(1,1-dimethylethoxy)carbonyl]-4-piperidinyl]carbonyl]amino]- <i>N</i> -[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 669 |
| 53a | 4-[[1-[(1,1-dimethylethoxy)carbonyl]-4-piperidinyl]carbonyl]amino]- <i>N</i> -[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 669 |
| 54 | 4-[(2,6-dichlorobenzoyl)amino]- <i>N</i> -[[2-(4-fluorophenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 648 |
| 55 | 4-[(2,6-dimethoxybenzoyl)amino]- <i>N</i> -[[2-(4-fluorophenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 640 |
| 59 | 4-[(4-piperidinylcarbonyl)amino]- <i>N</i> -[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 569 |
| 60 | 4-[[3-(3,5-dichloro-4-pyridinyl)carbonyl]amino]- <i>N</i> -[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 631 |
| 61 | 4-[[2-(dimethylamino)carbonyl]amino]- <i>N</i> -[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 529 |

| | | | |
|-----|---|-----|-----|
| 62a | O-[(2,6-dichlorophenyl)methyl]-3-fluoro- <i>N</i> -[[[(3 <i>S</i>)-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-tyrosine; | --- | 635 |
| 62b | O-[(2,6-dichlorophenyl)methyl]-3-fluoro- <i>N</i> -[[[(3 <i>R</i>)-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-D-tyrosine; | --- | 635 |
| 62c | O-[(2,6-dichlorophenyl)methyl]-3-fluoro- <i>N</i> -[[[(3 <i>S</i>)-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-D-tyrosine; | --- | 635 |
| 62d | O-[(2,6-dichlorophenyl)methyl]-3-fluoro- <i>N</i> -[[[(3 <i>R</i>)-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-tyrosine; | --- | 635 |
| 64 | 4-[(2,2-dimethyl-1-oxopropyl)amino]- <i>N</i> -[[[(3 <i>S</i>)-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 542 |
| 65 | 4-[[[(2-ethoxy-1-naphthalenyl)carbonyl]amino]- <i>N</i> -[[[(3 <i>S</i>)-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 656 |
| 67 | 4-[(cyclopropylcarbonyl)amino]- <i>N</i> -[[[(3 <i>S</i>)-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 526 |
| 68 | 4-[[[(2,2,3,3-tetramethylcyclopropyl)carbonyl]amino]- <i>N</i> -[[[(3 <i>S</i>)-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 582 |
| 69 | 4-[(2-methyl-1-oxopropyl)amino]- <i>N</i> -[[[(3 <i>S</i>)-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 528 |
| 70 | 4-[[[(3 <i>S</i>)-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]amino]- <i>N</i> -[[[(3 <i>S</i>)-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 735 |
| 72 | 4-[[[(1-methylcyclopropyl)carbonyl]amino]- <i>N</i> -[[[(3 <i>S</i>)-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine. | --- | 540 |

Example 2

4-(2,6-dimethoxyphenyl)-*N*-[[[(3*S*)-2-(phenylsulfonyl)-

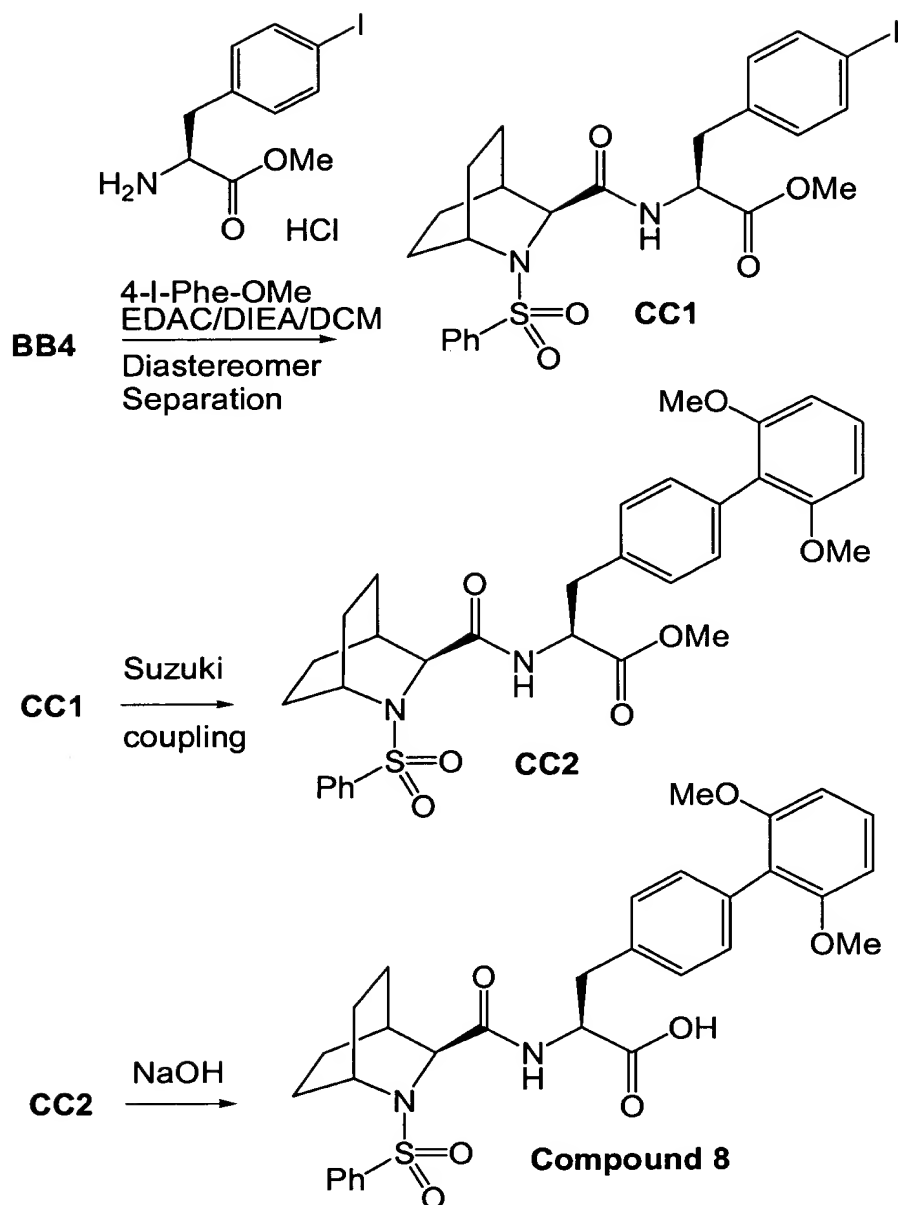
2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine, (Compound 8)

A mixture of Compound **BB4** (2.95 g, 1 eq, prepared as in Example 1), (*S*)-4-iodo-phenylalanine hydrochloride (3.40 g, 1 eq), EDAC hydrochloride (2.5 eq),

and DIEA (3 eq) in 50 mL DCM was stirred for 5 h at room temperature, washed sequentially with NaHCO_3 (sat'd, aq), 1 N HCl, dried (Na_2SO_4), and evaporated to give a white solid foam which was crystallized from hexane-ethyl acetate to yield colorless crystals of Compound **CC1** as the (S,S) diastereomer (55% yield). ^1H NMR (CDCl_3) 7.90 (d, $J=7$, 2H), 7.6 (m, 5H), 7.12 (d, $J=8$, 1H), 6.93 (d, $J=8$, 2H), 4.88 (q, $J=8$, 1H), 4.00 (d, $J=4$, 1H), 3.81 (d, $J=4$, 1H), 3.77 (s, 3H), 3.78 (dd, $J=14$ and 5, 1H), 3.02 (dd, $J=14$ and 7, 1H), 2.22 (m, 1H), 1.6-0.9 (m, 8H).

To a solution of Compound **CC1** (0.64 g) and 0.41 g 2,6-dimethoxyphenylboronic acid (2 eq) in 20 mL of dimethoxyethane under N_2 atmosphere was added 2 mL of 2N solution of K_2CO_3 (aq) followed by $\text{Pd}(\text{PPh}_3)_4$ (50 mg). The mixture was stirred 24 h at rt under N_2 atmosphere and purified by column chromatography (silica, 1:1 hexane:ethyl acetate). Compound **CC2** (0.22 g) was isolated as a white foam. ^1H NMR (CDCl_3) 7.91 (d, $J=7$, 2H), 7.8-7.1 (m, 9H), 6.63 (d, 8, 2H), 4.93 (m, 1H), 4.03 (m, 1H), 3.81 (s, 1H), 3.79 (s, 3H), 3.69 (s, 6H), 3.31 (dd, $J=14$ and 6, 1H), 3.05 (dd, $J=14$ and 9, 1H), 2.21 (m, 1H), 1.6-1.0 (m, 8H).

Compound **CC2** (0.2 g) was dissolved in 20 mL of MeOH and 3 mL 3N NaOH (aq). Reaction mixture was stirred overnight, then diluted with 50 mL H_2O , and washed with EtOAc. The aqueous layer was acidified to pH 2 with 1N HCl and extracted 3X with EtOAc. Organic layers were combined, dried over MgSO_4 , filtered and evaporated providing 0.12 g of Compound **8** as a white crystalline solid. (ESI) m/z 577 (free acid, M-H^-).



Using the procedure of Example 2 and the appropriate reagents and starting materials known to those skilled in the art, other compounds of the present invention may be prepared including, but not limited to:

| Cpd | | (M-H) ⁻ | (M+H) ⁺ |
|------------|---|--------------------|--------------------|
| 18 | 4-(2,6-dimethoxyphenyl)-N-[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | --- | 592 |
| 18a | 4-(2,6-dimethoxyphenyl)-N-[[[(3R)-2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 591 | 592 |
| 23 | 4-[[4-(1,1-dimethylethyl)phenyl]ethynyl]-N-[[2-[(4- | 611 | --- |

| | | | |
|----|--|-----|-----|
| | methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | | |
| 24 | 4-(phenylethynyl)- <i>N</i> -[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 555 | --- |
| 32 | 4-(1 <i>H</i> -pyrrol-1-yl)- <i>N</i> -[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 520 | --- |
| 33 | 4-phenyl- <i>N</i> -[[2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 531 | --- |
| 45 | <i>O</i> -(1,1-dimethylethyl)- <i>N</i> -[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-tyrosine; | --- | 516 |
| 46 | α (<i>S</i>)-[[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]amino]-benzenebutanoic acid; | --- | 457 |
| 58 | 4-(1,1-dimethylethyl)- <i>N</i> -[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine. | --- | 499 |

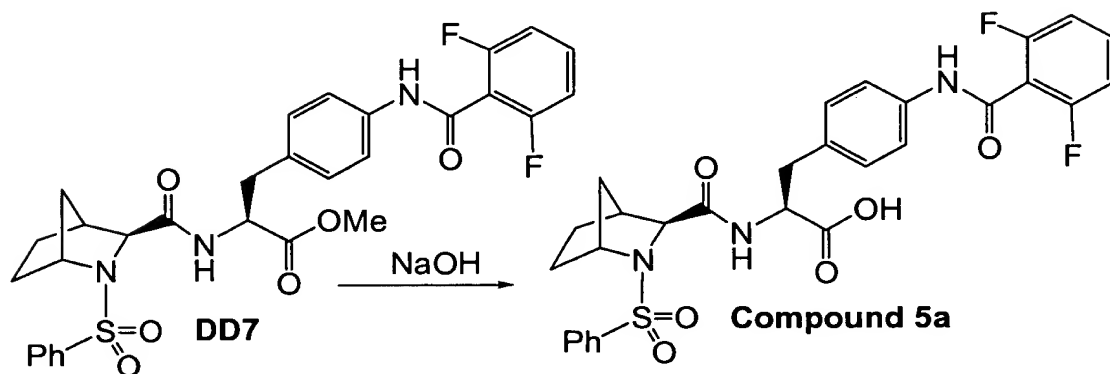
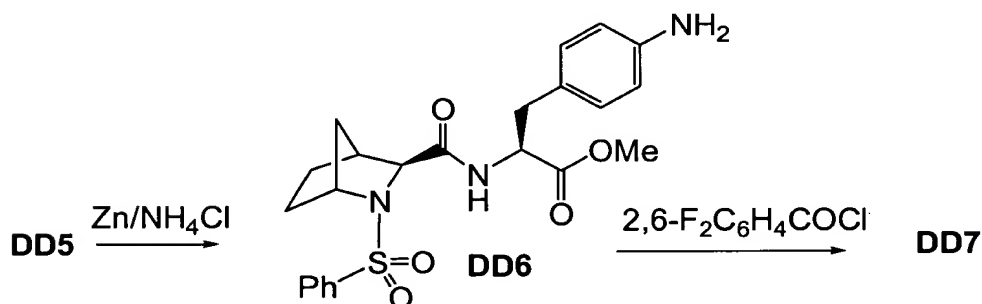
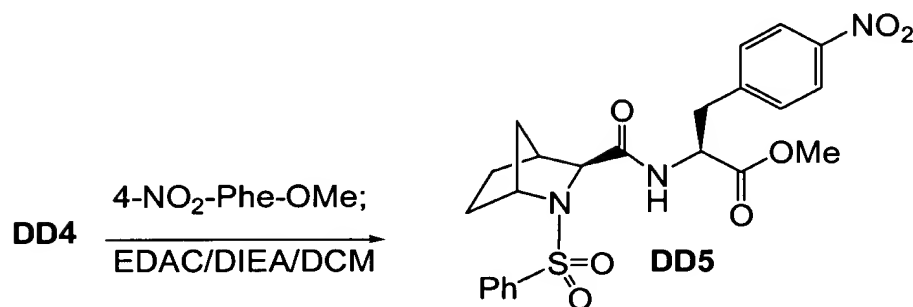
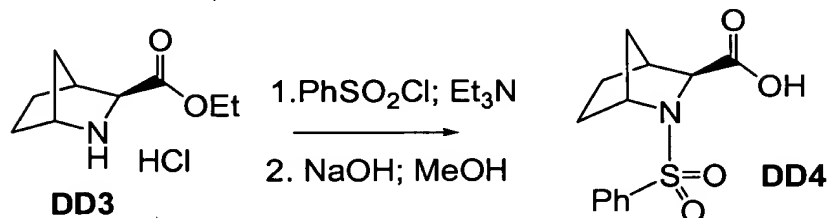
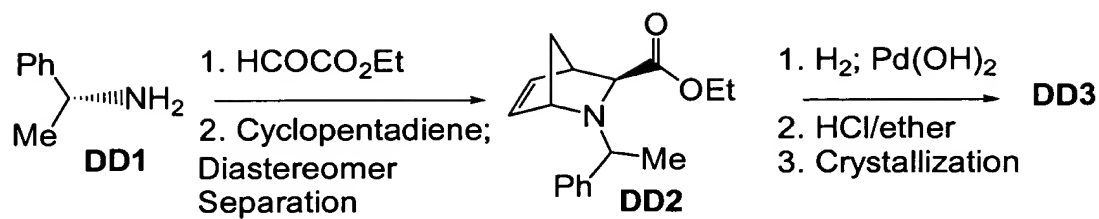
Example 3

4-[(2,6-difluorobenzoyl)amino]-*N*-[[2-(phenylsulfonyl)-2-azabicyclo[2.2.1]hept-3-yl]carbonyl]-L-phenylalanine (Compound **5a**)

(*R*)-(+)- α -methylbenzylamine Compound **DD1** (24.2 g, 0.2 M) was mixed with 40 mL of 50% solution of ethyl glyoxalate in toluene (0.2 M) and the toluene was removed in vacuo. A solution of the resulting residue in 150 mL of DMF, 50 mL of freshly distilled cyclopentadiene, 110 μ L of water and 14 mL of TFA was stirred at rt for 24 hr. The mixture was quenched with 50 mL of 1N NaHCO₃ (aq) and diluted with 400 mL of brine. The solution was extracted with ethyl acetate and the organic fraction was dried (MgSO₄) and concentrated. The diastereomers were separated by column chromatography (silica gel; EtOAc:hexane; 1:9) and Compound **DD2** (21 g, 40%) was isolated as a yellow oil. A mixture of 21 g of Compound **DD2** and 200 mg of Pd(OH)₂ in EtOH was hydrogenated for 24 hr and filtered through a celite pad. The filtrate was concentrated in vacuo, treated with 1N HCl in ether and concentrated. The residue was crystallized from DCM-ether to afford Compound **DD3** as white crystals (12.0 g). ¹H NMR (D₂O) 4.70 (s, 2H), 4.47 (q, J=7, 2H), 4.24 (s, 1H), 2.95 (m, 1H), 1.9-1.6 (m, 7H), 1.20 (t, J=7, 3H).

A solution of 2.21 g of Compound **DD3** in DCM (50 mL) containing Et₃N (2 eq.) was treated with benzenesulfonyl chloride (1.91 g). The mixture was stirred for 3 h, washed with 10% NaHCO₃ (aq) and concentrated. The residue was dissolved in 50 mL of MeOH and treated with 10 mL 3N NaOH (aq). The reaction was stirred for 12 hr and MeOH was removed in vacuo. The residue was dissolved in 100 mL H₂O, acidified with 1N HCl to a pH of ~ 2 and extracted with EtOAc to provide a white solid after evaporation. Recrystallization from hexane-EtAc provided a crystalline Compound **DD4** (2.5 g). The further transformations were performed using the procedure described in Example 1. Compound **5a** was obtained as a white solid: (ESI) *m/z* 582 (free acid, M-H⁻).

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Using the procedure of Example 3 and the appropriate reagents and starting materials known to those skilled in the art, other compounds of the present

invention may be prepared including, but not limited to:

| Cpd | | (M-H) | (M+H ⁺) |
|------------|--|-------|---------------------|
| 5b | 4-[(2,6-difluorobenzoyl)amino]- <i>N</i> -[[[(3 <i>R</i>)-2-(phenylsulfonyl)-2-azabicyclo[2.2.1]hept-3-yl]carbonyl]-L-phenylalanine; | 582 | --- |
| 16a | 4-[(2,6-dichlorobenzoyl)amino]- <i>N</i> -[[[(3 <i>S</i>)-2-(phenylsulfonyl)-2-azabicyclo[2.2.1]hept-3-yl]carbonyl]-L-phenylalanine; | 614 | --- |
| 16b | 4-[(2,6-dichlorobenzoyl)amino]- <i>N</i> -[[[(3 <i>R</i>)-2-(phenylsulfonyl)-2-azabicyclo[2.2.1]hept-3-yl]carbonyl]-L-phenylalanine; | 614 | 616 |
| 19a | 4-[(2,6-dimethoxybenzoyl)amino]- <i>N</i> -[[[(3 <i>S</i>)-2-(phenylsulfonyl)-2-azabicyclo[2.2.1]hept-3-yl]carbonyl]-L-phenylalanine; | 606 | 608 |
| 19b | 4-[(2,6-dimethoxybenzoyl)amino]- <i>N</i> -[[[(3 <i>R</i>)-2-(phenylsulfonyl)-2-azabicyclo[2.2.1]hept-3-yl]carbonyl]-L-phenylalanine. | 606 | --- |

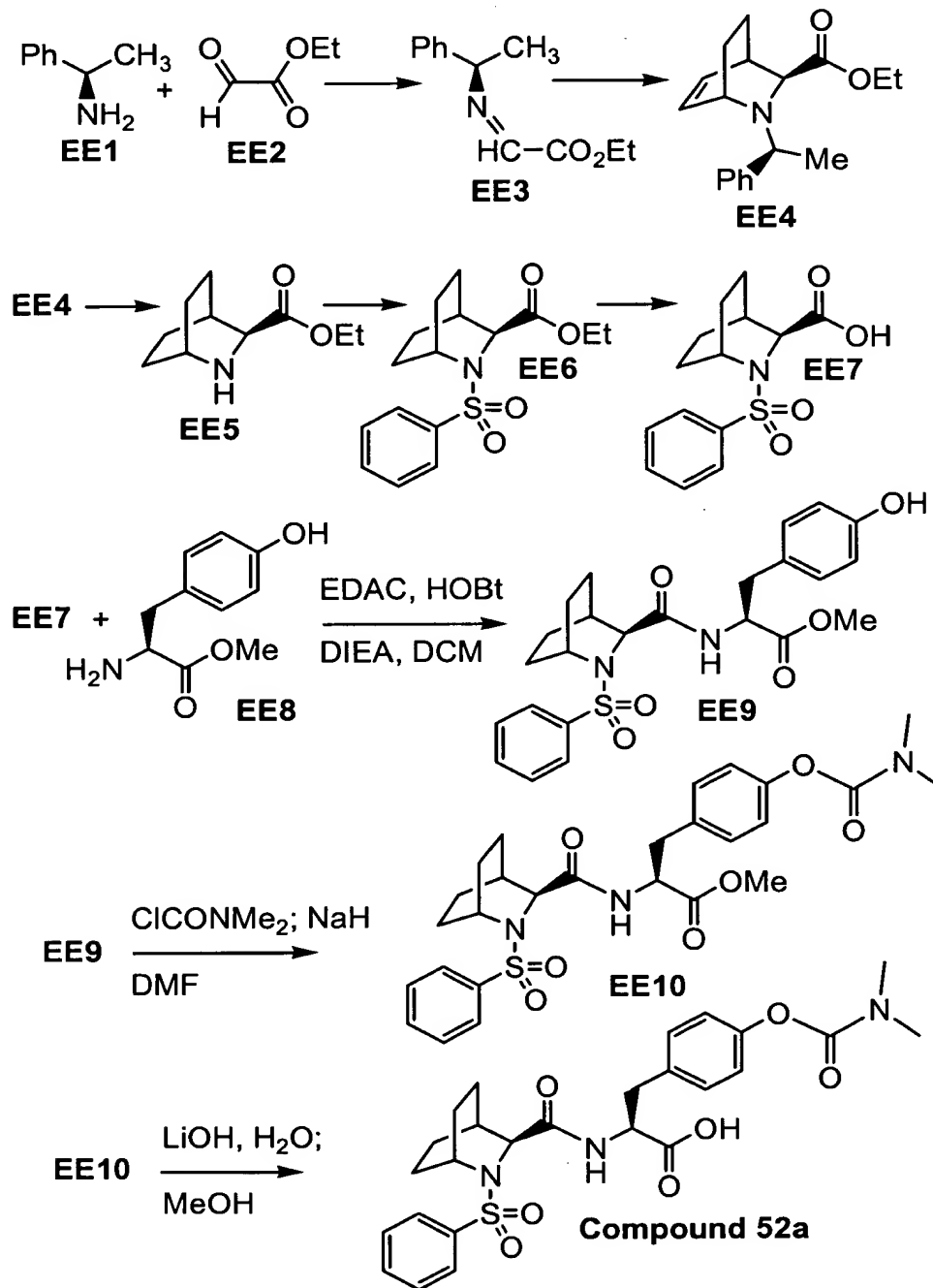
Example 4

O-[(dimethylamino)carbonyl]-*N*-[[[(3*S*)-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-tyrosine (Compound **52a**)

Compound **EE1**, the (*R*)-(+)- α -methylbenzylamine (12.1 g), was mixed with 20 mL 50% solution of ethyl glyoxalate in toluene (Fluka) Compound **EE2**. The reaction was stirred for 30 min and evaporated in vacuo resulting Compound **EE3** as a yellow viscous oil. The Compound **EE3** oil was dissolved in 300 mL of dry DCM and cooled down in dry ice/acetone bath (N₂ atmosphere). TFA (6 mL, 8.81 g) was added dropwise followed by BF₃ diethyl etherate (12 mL, 13.5 g). The reaction mixture was stirred for 10 min and 1,3-cyclohexadiene (15 mL) was added dropwise over 30 min period. The reaction was kept in the cooling bath for 3 h, warmed up to rt and stirred for 24 h. The resulting mixture was washed with NaHCO₃ 10% aq and evaporated. The residue was subjected to column chromatography (silica, hexane/EtOAc 9:1) providing Compound **EE4** as a colorless oil (15.1 g). ¹H NMR (CDCl₃) 7.49-7.40 (m, 2H), 7.27-7.15 (m, 3H), 6.39 (t, J=7, 1H), 6.26 (t, J=5, 1H), 4.20 (q, J=7, 2H), 3.61 (m, 1H), 3.60 (q, J=3, 1H), 2.89 (m, 1H), 2.73 (m, 1H), 2.1-2.0 (m, 1H), 1.63-1.58 (m, 1H), 1.59 (d, J=3, 3H), 1.11 (t, J=7, 3H), 1.3-1.0 (m, 2H).

The suspension of Compound **EE4** with 10% Pd/carbon (200 mg) in 200 mL of EtOH was hydrogenated for 24 h (30 psi, rt). The reaction mixture was filtered through celite and concentrated in vacuo providing Compound **EE5** as a colorless oil. The solution of Compound **EE5** (1.83 g, 0.01 mol) in DCM (100 mL) and Et₃N (280 μ l, 2 eq) at 0°C was treated with PhSO₂Cl (1.77 g, 1 eq) in 20 mL DCM dropwise over 1 h. The ice bath was removed and the mixture stirred for 18 h. The mixture was washed with water (200 mL), 0.1 N HCl, 1 N NaHCO₃, dried over MgSO₄ and evaporated. The residue was recrystallized from hexane-EtOAc providing Compound **EE6** as a white solid (2.58 g, 80%). The ethyl ester was hydrolyzed using NaOH to provide the acid Compound **EE7**. The acid Compound **EE7** (590 mg, 0.002 mol), L- tyrosine methyl ester Compound **EEH** (400 mg, 0.00205 mol), EDAC (767 mg, 2 eq) and HOBt (540 mg, 2 eq) were dissolved in 10 mL of dry DCM containing 350 μ L of DIEA. The solution was stirred at room temperature overnight. The resulting reaction mixture was washed sequentially by NaHCO₃ aq. solution, 0.1 N HCl and water, dried and evaporated. The residue was subjected by column chromatography (silica, hexane/EtOAc 1:1) providing Compound **EE9** (white solidified foam, 550 mg, 58% yield). A suspension of NaH (84 mg of 60% suspension in oil, washed by hexane) was treated by 10 mL DMF solution of 550 mg of Compound **EE9** at 0° C followed by 100 μ l of dimethyl carbamoyl chloride. The mixture was allowed to warm up to room temperature and was stirred overnight. The resulting reaction mixture was diluted by 100 mL of ethyl acetate, washed by NaCl (sat'd aq) and evaporated. The oil was purified by column chromatography (silica, hexane/EtOAc 1:1) to afford 510 mg of Compound **EE10**. A solution of 500 mg of Compound **EE10** in 20 mL mixture MeOH: water 10:1 was treated with 60 mg LiOH hydrate. The reaction mixture was stirred 24 hr at room temperature, diluted with 100 mL water and extracted by EtOAc. The organic layer was discarded. The aqueous layer was acidified to pH 2 with 2N HCl (aq), then extracted 3 times with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated to yield 420 mg of Compound **52a**. The solid material was crystallized from hexane-EtOAc providing 350 mg of pure material. ¹H NMR (CDCl₃) 7.90 (d, J=9, 2H), 7.65-7.50 (m, 3H), 7.35-7.20 (m, 3H), 7.08-

7.00 (m, 3H), 4.92-4.85 (m, 1H), 4.05 (broad s, 1H), 3.81 (broad s, 1H), 3.38 (dd, $J = 15$ and 9 , 1H), 3.10-3.00 (m, 7H), 2.17 (broad s, 1H), 1.60-1.00 (m, 8H). (ESI) m/z 530 ($M+H^+$).



Using the procedure of Example 4 and the appropriate reagents and starting materials known to those skilled in the art, other compounds of the present

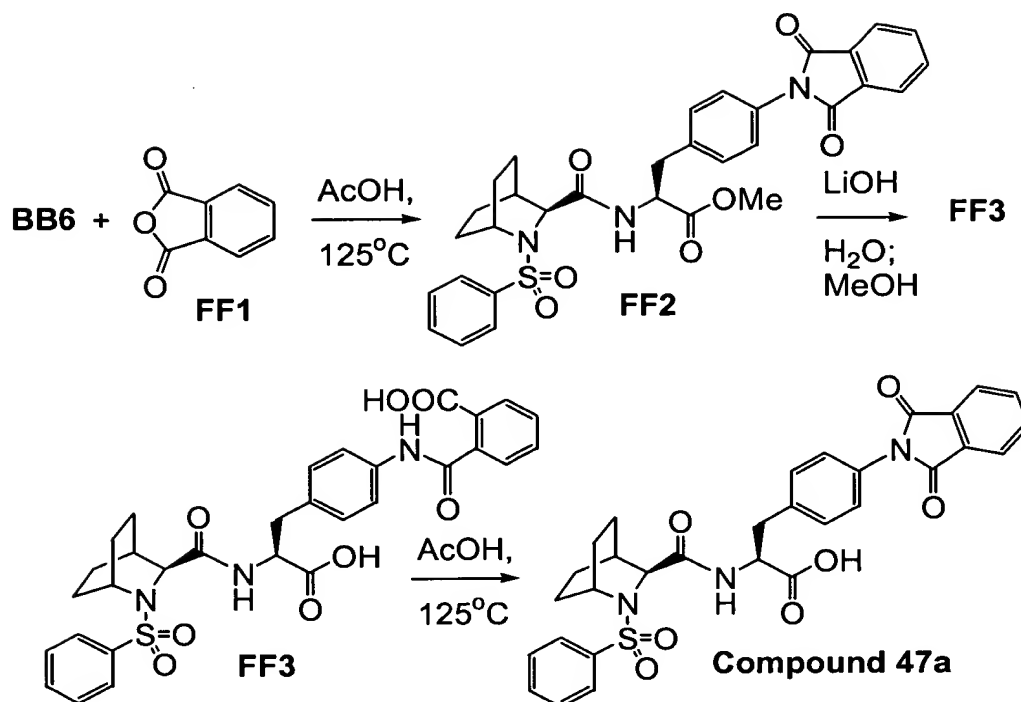
invention may be prepared including, but not limited to:

| Cpd | | (M+H ⁺) |
|-----|---|---------------------|
| 52 | O-[(dimethylamino)carbonyl]- <i>N</i> -[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-tyrosine; | 530 |
| 56 | O-(4-morpholinylcarbonyl)- <i>N</i> -[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-tyrosine; | 572 |
| 57 | O-[[bis(1-methylethyl)amino]carbonyl]- <i>N</i> -[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-tyrosine. | 586 |

Example 5

4-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-*N*-[[*(3S)*-2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine (Compound **47a**)

A solution of Compound **BB6** (prepared as described in Example 1) (471 mg, 0.001 mol) and phthalic anhydride Compound **FF1** (150 mg, 0.001 mol) in 10 mL AcOH was heated in the sealed tube at 120°C for 3 h and cooled to rt. The resulting solution was diluted by 200 mL H₂O and extracted several times by EtOAc. The organic layers were combined, washed with sat'd NaHCO₃ and evaporated. The residue was subjected to column chromatography (silica, hexane:EtOAc, 1:1) providing 450 mg of Compound **FF2**. Basic hydrolysis (described in the previous examples) resulted in 400 mg of a white solid material (Compound **FF3**) which was subjected to cyclization without purification. A solution of Compound **FF3** (400 mg) in 5 mL AcOH was heated in the sealed tube at 120°C for 2 h, diluted by 200 mL H₂O and extracted several times by EtOAc. The organic layers were combined, washed by H₂O and concentrated. Column chromatography (silica, CHCl₃/MeOH/AcOH 90:9:1) provided 200 mg of white solid Compound **47a**. ¹H NMR (DMSO) 8.1 (m, 1H), 7.97-7.88 (m, 6H), 7.68-7.56 (m, 3H), 7.41 (d, J=8, 2H), 7.34 (d, J=8, 2H), 4.5 (m, 1H), 4.21 (s, 1H), 3.58 (s, 1H), 3.15-3.00 (m, 2H), 2.02 (s, 1H), 1.90-1.70 (m, 1H), 1.50-1.00 (m, 8H). (ESI) *m/z* 588 (M+H⁺).



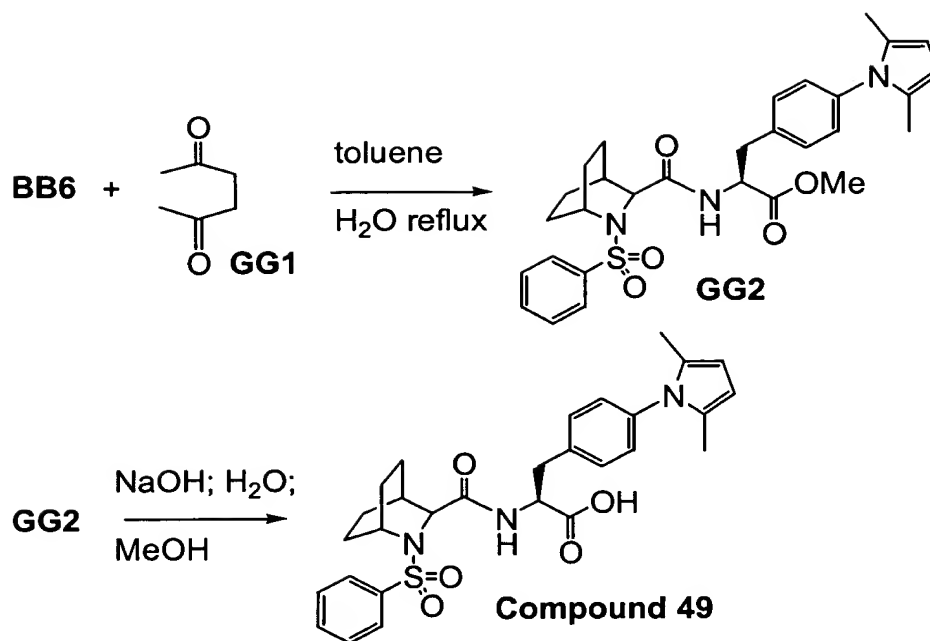
Using the procedure of Example 5 and the appropriate reagents and starting materials known to those skilled in the art, other compounds of the present invention may be prepared including, but not limited to:

| Cpd | | (M+H ⁺) |
|-----|--|---------------------|
| 47 | 4-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-N-[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine. | 588 |

Example 6

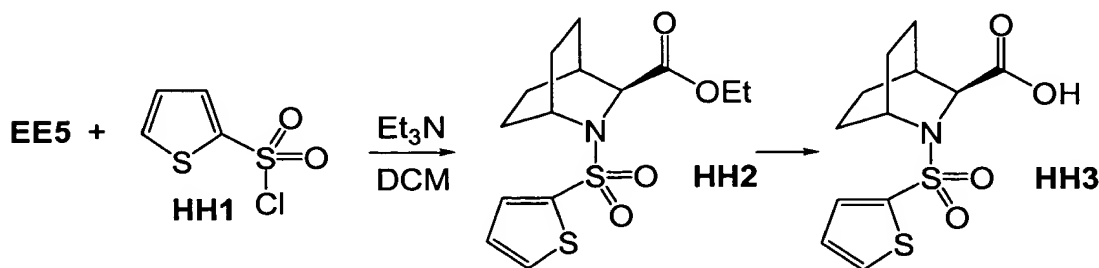
4-(2,5-dimethyl-1H-pyrrol-1-yl)-N-[[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; (Compound 49)

Compound BB6 (using the racemate prepared as described in Example 1) (300 mg, 0.00064 mol) and 2,5-hexanedione Compound GG1 (300 mg, 0.0026 mol) in 80 mL toluene was refluxed with a Dean-Stark trap overnight and cooled to rt. The resulting solution was evaporated and the residue was subjected to column chromatography (silica, hexane:EtOAc, 1:1) providing 320 mg of Compound GG2. Basic hydrolysis (described in the previous examples) resulted in 250 mg of Compound 49, a white solid material. (ESI) *m/z* 536 (M+H⁺).



Example 7

Compound **EE5** (prepared as described in Example 4) (1.83 g, 0.001 mol) in DCM (100 mL) and Et_3N (280 μL , 2 eq) at 0°C was treated with 2-thiophenesulfonyl chloride Compound **HH1** (2.35 g, 1.3 eq) neat as one portion. The ice bath was removed and the mixture stirred for 24 h. The mixture was washed with water (200 mL), 0.1 N HCl, 1 N NaHCO_3 , dried over MgSO_4 and evaporated. The residue was purified by column chromatography (silica, hexane:EtOAc, 1:1) and recrystallized from hexane-EtOAc to provide Compound **HH2** as white solid (1.97 g, 60%). The ethyl ester was hydrolyzed using NaOH to provide the acid Compound **HH3**. Compound **HH3** was used to replace Compound **BB4** or Compound **EE7** to obtain other compounds of the invention.



Using the procedure of Example 7 and the appropriate reagents and starting

materials known to those skilled in the art, other compounds of the present invention may be prepared including, but not limited to:

| Cpd | | (M+H ⁺) |
|-----|---|---------------------|
| 63 | O-[(dimethylamino)carbonyl]-N-[[2-(2-thienylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-tyrosine; | 536 |
| 66 | 4-[(2,6-dichlorobenzoyl)amino]-N-[[2-(2-thienylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 636 |
| 71 | 4-[[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-[[2-(2-thienylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine; | 637 |
| 71a | 4-[[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-[[[(3S)-2-(2-thienylsulfonyl)-2-azabicyclo[2.2.2]oct-3-yl]carbonyl]-L-phenylalanine. | 637 |

Biological Experimental Examples

As demonstrated by biological studies described hereinafter, and shown in Table III and Table IV, the compounds of the present invention are $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin receptor antagonists useful in treating integrin mediated disorders including, but not limited to, inflammatory, autoimmune and cell-proliferative disorders.

Ramos Cell Adhesion Assay ($\alpha_4\beta_1$ Mediated Adhesion / VCAM-1)

Immulon 96 well plates (Dynex) were coated with 100 μ L recombinant hVCAM-1 at 4.0 μ g/mL in 0.05 M NaCO₃ buffer pH 9.0 overnight at 4° C (R&D Systems). Plates were washed 3 times in PBS with 1 % BSA and blocked for 1 h @ room temperature in this buffer. PBS was removed and compounds to be tested (50 μ L) were added at 2X concentration. Ramos cells, (50 μ L at 2 X 10⁶/mL) labeled with 5 μ M Calcein AM (Molecular Probes) for 1 h at 37 °C, were added to each well and allowed to adhere for 1 h at room temperature. Plates were washed 3 X in PBS + 1 % BSA and cells were lysed for 15 minutes in 100 μ L of 1 M Tris pH 8.0 with 1 % SDS. The plate was read at 485 nm excitation and 530 nm emission.

$\alpha_4\beta_7$ -K562 Cell Adhesion Assay ($\alpha_4\beta_7$ Mediated Adhesion / VCAM-1)

Immulon 96 well plates (Dynex) were coated with 100 μ L recombinant hVCAM-1 at 4.0 μ g/mL in 0.05 M NaCO₃ buffer pH 9.0 overnight at 4°C (R&D Systems). Plates were washed 3 times in PBS with 1 % BSA and blocked for 1 h @ room temperature in this buffer. PBS was removed and compounds to be tested (50 μ L) were added at 2X concentration. A stable cell line of K562 cells expressing human $\alpha_4\beta_7$, (50 μ L at 2 X 10⁶/mL) labeled with 5 μ M Calcein AM (Molecular Probes) for 1 h at 37 °C, were added to each well and allowed to adhere for 1 h at room temperature. Plates were washed 3 X in PBS + 1 % BSA and cells were lysed for 15 minutes in 100 μ L of 1 M Tris pH 8.0 with 1 % SDS. The plate was read at 485 nm excitation and 530 nm emission.

TABLE III
Inhibition of Binding of Ramos Cells to Immobilized VCAM-1

| Cpd | IC ₅₀ (nM) | Cpd | IC ₅₀ (nM) | Cpd | IC ₅₀ (nM) |
|-----|-----------------------|-----|-----------------------|-----|-----------------------|
| 1 | 45 | 28 | 1600 | 52a | 40 |
| 2 | 51 | 29 | 58 | 53 | 67 |
| 3 | 50 | 30 | >5 μ M | 53a | 219 |
| 5a | 81 | 31 | >5 μ M | 54 | 146 |
| 5b | 394 | 32 | >5 μ M | 55 | 303 |
| 6 | 25 | 33 | >5 μ M | 56 | 139 |
| 6a | 21 | 34 | >5 μ M | 57 | 757 |
| 6b | 222 | 35 | >5 μ M | 58 | 523 |
| 8 | 81 | 36 | >5 μ M | 59 | 237 |
| 9 | 267 | 37 | >5 μ M | 60 | 9 |
| 10 | 145 | 38 | >5 μ M | 61 | 56 |
| 11 | 179 | 39 | >5 μ M | 62 | >5 μ M |
| 12 | 104 | 40 | 293 | 62a | >5 μ M |
| 13 | 119 | 41 | >5 μ M | 63 | 112 |
| 14 | 160 | 42 | 22 | 64 | 393 |
| 15 | 67 | 43 | 103 | 65 | 193 |
| 16a | 153 | 44 | 309 | 66 | 17 |

| | | | | | |
|-----|------|-----|------------|-----|-----|
| 16b | 240 | 45 | 3165 | 67 | 628 |
| 18 | 124 | 46 | >5 μ M | 68 | 873 |
| 18b | 857 | 47 | 74 | 69 | 455 |
| 19a | 300 | 47a | 26 | 70 | 370 |
| 19b | 1210 | 48 | >5 μ M | 71 | 7 |
| 23 | 1420 | 49 | >5 μ M | 71a | 360 |
| 24 | 1100 | 50 | 55 | 72 | 4 |
| 25 | 903 | 50a | 54 | | |
| 26 | 669 | 51 | 784 | | |
| 27 | 1090 | 52 | 124 | | |

TABLE IV**Inhibition of Binding of K562 Cells to Immobilized VCAM-1**

| Cpd | IC ₅₀ (nM) | Cpd | IC ₅₀ (nM) | Cpd | IC ₅₀ (nM) |
|-----|-----------------------|-----|-----------------------|-----|-----------------------|
| 1 | 142 | 28 | >5 μ M | 52a | 436 |
| 2 | 98 | 29 | 4940 | 53 | 871 |
| 3 | 1945 | 30 | >10 μ M | 53a | 693 |
| 5a | 62 | 31 | >10 μ M | 54 | 118 |
| 5b | 3380 | 32 | >10 μ M | 55 | 91 |
| 6 | 283 | 33 | >10 μ M | 56 | 47 |
| 6a | 217 | 34 | >10 μ M | 57 | >5 μ M |
| 6b | 421 | 35 | >10 μ M | 58 | >10 μ M |
| 8 | 343 | 36 | >10 μ M | 59 | 1500 |
| 9 | >5 μ M | 37 | >10 μ M | 60 | --- |
| 10 | 4410 | 38 | >10 μ M | 61 | --- |
| 11 | 1490 | 39 | >10 μ M | 62 | >10 μ M |
| 12 | 1080 | 40 | 2510 | 62a | >10 μ M |
| 13 | >10 μ M | 41 | >10 μ M | 63 | 286 |
| 14 | 913 | 42 | 279 | 64 | >10 μ M |
| 15 | 1390 | 43 | 442 | 65 | 394 |
| 16a | 2090 | 44 | --- | 66 | 186 |

| | | | | | |
|------------|-------------|------------|-------------|------------|-------------|
| 16b | 393 | 45 | >10 μ M | 67 | 683 |
| 18 | 210 | 46 | >10 μ M | 68 | >50 μ M |
| 18a | 9000 | 47 | 83 | 69 | 1670 |
| 19a | 3822 | 47a | 102 | 70 | 2035 |
| 19b | 3220 | 48 | >10 μ M | 71 | 30 |
| 23 | >10 μ M | 49 | >10 μ M | 71a | 33 |
| 24 | >10 μ M | 50 | 810 | 72 | --- |
| 25 | >10 μ M | 50a | 223 | | |
| 26 | >10 μ M | 51 | >5 μ M | | |
| 27 | >10 μ M | 52 | 998 | | |

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

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